

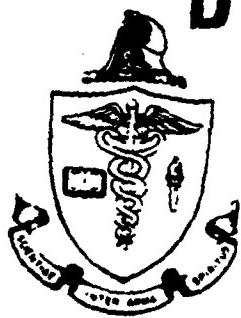
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# ANNUAL PROGRESS REPORT

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FY-89

VOLUME 2

PP 1-236



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DEPARTMENT OF CLINICAL INVESTIGATION  
WALTER REED ARMY MEDICAL CENTER  
WASHINGTON, D. C. 20307 - 5001  
CLINICAL INVESTIGATION PROGRAM  
RCS MED-300 (RI)

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SECURITY CLASSIFICATION OF THIS PAGE

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## REPORT DOCUMENTATION PAGE

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19. ABSTRACT (Continue on reverse if necessary and identify by block number)			
<p>This annual report identifies approved clinical research activities conducted at WRAMC (during FY89) which were approved and reviewed annually by the Human Use Committee/ Institutional Review Board or the Animal Use Committee as appropriate. A Detail Summary for each protocol, a list of publications and presentations are enclosed. Keywords:</p>			
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REPORT DATE: 04/30/89

WORK UNIT # 1151

DETAIL SUMMARY SHEET

TITLE: Evaluation of Renal Function, Protein Excretion and the Urinary Sediment in Patients with Antibody to the Human Immunodeficiency Virus (HIV)

KEYWORDS: urinalysis, kidney, HIV

PRINCIPAL INVESTIGATOR: Link, Christine CPT MC

ASSOCIATES: Moore, Jack LTC MC; Baker, James MAJ MC

DEPARTMENT: HIV Research

STATUS: Ongoing

APPROVAL DATE: Mar 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To describe the renal function, protein excretion, and urinary sediment in patients positive to HIV antibody; and to determine if any abnormalities found are related to the severity of disease.

TECHNICAL APPROACH

After informed consent, three urine samples are obtained. These are used to examine the urinary sediment, and to determine ability to acidify and concentrate urine after overnight fast. A 24-hour collection is used to determine creatinine clearance, total protein, and microalbuminuria. There has been no modification of the original protocol.

PRIOR AND CURRENT PROGRESS

From April 1987 through May 1988, 59 patients have been entered in the study. No patients have been withdrawn, and there have been no adverse reactions. The majority of patients have completed all portions of the study. The ELISA for urinary albumin determination has been developed. All submitted urines were tested. A manuscript is being written.

CONCLUSIONS

Abnormalities of tubular function (acidification and concentration) were most frequent, followed by urinalysis abnormalities. No patients had significant proteinuria or renal insufficiency. There was no relationship between the severity of the HIV disease and frequency of abnormalities.

REPORT DATE: 06/12/89

WORK UNIT # 1948

DETAIL SUMMARY SHEET

TITLE: A Double Blind Randomized Placebo-Controlled Trial of Fansidar Prophylaxis in Patients with HTLV-III Disease (WR Stage 5)

KEYWORDS: prophylaxis, pneumocystis, HIV

PRINCIPAL INVESTIGATOR: Wright, Craig MAJ MC

ASSOCIATES: Lennox, Jeffrey

DEPARTMENT: HIV Research

STATUS: Completed

APPROVAL DATE: Nov 1986

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To see if Fansidar prophylaxis once a week will prevent pneumocystis carinii pneumonia (PCP) in T helper cell deficient HIV infected patients with either thrush or anergy (Walter Reed Stage WR-5)

TECHNICAL APPROACH

Walter Reed Stage WR-5 patients are randomized to either receive placebo or Fansidar once a week and monitored for toxicity or the occurrence of pneumocystis pneumonia.

PRIOR AND CURRENT PROGRESS

Twenty-six patients were entered prior to the end of the study. Fourteen received Fansidar and twelve received placebo. Four cases of pneumocystis carinii pneumonia developed in the placebo group. No cases of PCP in the Fansidar group. Four patients, all in the Fansidar group, were withdrawn for presumed hematologic toxicity of the study drug.

CONCLUSIONS

1) Fansidar is effective as a chemoprophylactic agent against first episode of PCP. 2) Minor hematologic toxicity is associated with Fansidar prophylaxis.

REPORT DATE: 10/20/89

WORK UNIT # 1951

DETAIL SUMMARY SHEET

TITLE: Human Immune Response to HTLV-III Infection

KEYWORDS: cytotoxic T cells, HIV, immunology

PRINCIPAL INVESTIGATOR: Rhoads, Joanne MAJ MC

DEPARTMENT: HIV Research

STATUS: Completed  
APPROVAL DATE: Dec 1986

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To evaluate HIV specific T memory lymphocyte responses of human peripheral blood lymphocytes of HIV infected patients.

TECHNICAL APPROACH

Donor B cells are transformed with EVB and either coated HIV antigen or infected with HIV-vaccinia hybrid to use for targets for HLA restricted cytotoxic T cells from the same patients.

PRIOR AND CURRENT PROGRESS

There has been no activity in this protocol since October, 1988.

CONCLUSIONS

Recommend this study be listed as completed.

STATEMENT "A" per Jan Kinsey  
Dept. Of Clinical Investigation/HSHL-CI  
Walter Reed Army Medical Center  
Washington, DC 20307-5001  
TELECON 5/16/90

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REPORT DATE: 09/08/89

WORK UNIT # 1952

DETAIL SUMMARY SHEET

TITLE: The Clinical Presentation of HIV Infected Patients at Walter Reed Army Medical Center

KEYWORDS: HIV, epidemiology, disease progression

PRINCIPAL INVESTIGATOR: Oster, Charles COL MC

ASSOCIATES: Rhoads, Joanne MAJ MC; Birx, Deborah MAJ MC

DEPARTMENT: HIV Research

STATUS: Ongoing

APPROVAL DATE: Jan 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To evaluate clinical and laboratory data on the first 402 adults seen in clinic at WRAMC who are infected with HIV-I by retrospectively reviewing their records.

TECHNICAL APPROACH

Chart review of medical records and laboratory studies on HIV infected patients.

PRIOR AND CURRENT PROGRESS

Nothing was done on this study in FY 89 but we anticipate chart review to begin soon.

CONCLUSIONS

No conclusions have been reached, request that the study remain open as chart review will begin soon.

REPORT DATE: 01/04/89

WORK UNIT # 1953

DETAIL SUMMARY SHEET

TITLE: The Generation of Human Monoclonal Antibodies to the HIV

KEYWORDS: monoclonal, HIV

PRINCIPAL INVESTIGATOR: Drabick, Joseph CPT MC

ASSOCIATES: Baker, James MAJ MC

DEPARTMENT: HIV Research

STATUS: Ongoing  
APPROVAL DATE: Jan 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

The purpose of this study is to generate human monoclonal antibodies to commercially available recombinant HIV antigen from the lymphocytes of patients infected with HIV.

TECHNICAL APPROACH

B. lymphocytes from peripheral blood or available lymphoid tissues are separated then transformed with EBV. The transformed lymphocytes are screened for antibodies to HIV, recombinant HIV antigens and recombinant soluble CD4. Positive wells are fused to heteromyeloma SHM-D33-0 and screened for specific antibody production.

PRIOR AND CURRENT PROGRESS

There have been no published reports of the production of human monoclonals to HIV to date. To our knowledge no group is attempting to manufacture an anti-CD4 monoclonal. Fourteen (14) patients have been entered in the project to date. In all cases the source of B lymphocytes has been peripheral blood, due to an unavailability of other lymphoid tissues. Initial screening of EBV transformed B cells of the latest 2 patients have revealed antibodies to gp120, p24/55, gp412 and CD4. Fusions of these secretors are currently in progress.

CONCLUSIONS

We are currently optimistic about success with the current batch given the excellent results so far. Utilizing the same process we have been successful in making monoclonals to malaria and bacterial pathogens. We were especially pleased with the detection of anti-Cd4 antibodies in preliminary screening. No further changes in financing or other modifications are anticipated.

REPORT DATE: 05/10/89

WORK UNIT # 1955

DETAIL SUMMARY SHEET

TITLE: T Helper Cell Depleted Mouse Model to Study Immunopathogenesis and  
Immunotherapy in AIDS

KEYWORDS: AIDS, T helper cells, immunodeficiency

PRINCIPAL INVESTIGATOR: Hoover, David MAJ MC

DEPARTMENT: HIV Research

STATUS: Completed

APPROVAL DATE: Mar 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

Examine immunological function of mice depleted of T helper cells.

TECHNICAL APPROACH

Mice are depleted of T helper cells by treatment with anti-L3T4. They are then challenged with pathogenic organisms and their immune responses examined by in vitro techniques and by survival analysis.

PRIOR AND CURRENT PROGRESS

None. This project was not funded.

CONCLUSIONS

None.

REPORT DATE: 08/21/89

WORK UNIT # 1958

DETAIL SUMMARY SHEET

TITLE: In Situ Hybridization for Detection of HIV in Langerhans Cells of HIV Infected Patients

KEYWORDS: HIV, Langerhans cells, macrophages

PRINCIPAL INVESTIGATOR: Hoover, David LTC MC

ASSOCIATES: Kalter, Chester MD

DEPARTMENT: HIV Research

STATUS: Ongoing

APPROVAL DATE: Jul 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

a) Determine whether HIV genome is present in Langerhans cells of the skin; b) Correlate percentage of infected Langerhans cells with degree of immunosuppression related to HIV infection and with infection on blood monocytes.

TECHNICAL APPROACH

Samples of normal skin will be examined by in situ hybridization for HIV and immunohistochemical methods to mark Langerhans cells. The percentage of HIV-infected Langerhans cells will be correlated with clinical stage as determined by the Walter Reed staging system.

PRIOR AND CURRENT PROGRESS

Total enrollment to date included 8 patients and 3 controls. Current data has been negative for evidence of HIV in the epidermis by in situ hybridization, macrophage coculture, electron microscopy, P24 antigen capture or reverse transcriptase assay. Immunofluorescent assay for Langerhans cells reveals no significant decrease in number in HIV+ patients (n=3). The biopsy techniques appear to be well tolerated, and no patients have withdrawn from the study. The patients do not benefit directly from involvement in the study.

CONCLUSIONS

Early findings indicate that HIV is difficult to detect in the skin (whether random or lesional biopsy) if present at all. More samples need to be analyzed by various methods and more sensitive techniques.

REPORT DATE: 01/08/90

WORK UNIT # 3342

DETAIL SUMMARY SHEET

TITLE: Delayed Type Hypersensitivity Skin Testing: Correlation of Intradermal Injection Vs. Epicutaneous Antigen Placement and CD4 Number in Normals and HIV Seropositive Subjects

KEYWORDS: DTH, skin testing, multitest

PRINCIPAL INVESTIGATOR: Birx, Deborah MAJ MC

DEPARTMENT: HIV Research

STATUS: Ongoing

APPROVAL DATE: Aug 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

Correlate antigen reactivity by intradermal and epicutaneous injection to circ. CD4 number. Compare subject reactivity to each of the antigens: Tetanus, Candida, Trichophyton IC/Multitest Correlate anergy by multitest and ID injection with evidence of HIV disease progression. Develop a standardized anergy panel to clinical staging of HIV infected patients.

TECHNICAL APPROACH

Simultaneous application of the multitest and ID injection of antigens in HIV infected patients.

PRIOR AND CURRENT PROGRESS

Protocol had to be approved by the human use committee at the USUHS which was not received until the mid-1989. Subsequently, the protocol nurses at WRAMC have received the consent form and plan to begin enrolling patients. No patients have been enrolled at this date.

CONCLUSIONS

No conclusions can be reached because the protocol is just beginning.

REPORT DATE: 07/05/89

WORK UNIT # 6218

DETAIL SUMMARY SHEET

TITLE: Evaluation of Human Immunodeficiency Virus Related Proteins on the Surface of Lymphocytes from Children with Evidence of HIV Exposure or HIV Illnesses

KEYWORDS: flowcytometry, HIV antigen, mononuclear cell

PRINCIPAL INVESTIGATOR: Fischer, Gerald COL MC

ASSOCIATES: Baker, James MAJ MC; Zwadsky, Peter COL MC

DEPARTMENT: HIV Research

STATUS: Ongoing

APPROVAL DATE: May 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

The purpose of this study is to examine the presence of HIV antigen on different mononuclear cell populations in infants and children to evaluate its use in determining in vivo distribution of HIV in various cell lineages.

TECHNICAL APPROACH

Mononuclear cells are harvested from 1cc to 3cc of heparinized whole blood using standard methods. The mononuclear fraction is diluted to 10<sup>7</sup> cells and paired aliquots are incubated with anti-leu 3a PE anti-leu 4 PE and in selected cases, anti-leu M3 PE. These paired samples are then incubated with murine monoclonal anti-GP120 or anti-P24 and goat anti-muine IgG FITC. The samples and control specimens are then analyzed using FACS analysis.

PRIOR AND CURRENT PROGRESS

We have enrolled 22 patients and performed 40 studies. We identified P24 antigen in CD3 positive and CD4 positive cells on 4 occasions in 2 patients. Both of these patients had symptomatic HIV disease, were HIV culture positive and had free P24 antigen by ELISA. GP120 was not identified on CD3 or CD4 positive cells. We also identified monocyte populations bearing P24 or GP120 antigen. In most cases, both P24 and GP120 were present together and the positive monocyte populations tended to be larger than positive T cell populations. Positive populations were more frequently encountered among patients with more advanced disease. However, not all patients with AIDS or detectable serum P24 antigen had consistently positive mononuclear cell populations.

CONCLUSIONS

We conclude that the determination of mononuclear cell associated HIV antigens identified in this manner represents a promising technique and should be further evaluated to establish sensitivity, specificity and correlation to disease activity.

REPORT DATE: 06/29/89

WORK UNIT # 6220

DETAIL SUMMARY SHEET

TITLE: Epidemiology of HIV In Pediatric and Perinatal Patients - A Natural History Study

KEYWORDS: immunodeficiency, pediatrics, epidemiology

PRINCIPAL INVESTIGATOR: Fischer, Gerald COL MC

ASSOCIATES: Pettett, Gary COL MC; Scott, Robert COL MC

DEPARTMENT: HIV Research

STATUS: Ongoing

APPROVAL DATE: Jul 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

The purpose of this study is to develop a Military Pediatric HIV Program for identification of military dependents (spouses and children) of HIV infected personnel. The study will identify basic epidemiologic information and follow these high risk or HIV-infected children over time to assess infection status and disease progression.

TECHNICAL APPROACH

The Military Pediatric HIV Program will identify children at high risk for HIV infection by matching USAHDS reports with the computer linked DEERS data files. All families with one or both spouses infected with HIV will be offered voluntary enrollment in this program. In addition, children with illness or other problems associated with HIV infection may also be voluntarily enrolled in this study. All children followed will be periodically reevaluated using state-of-the art HIV diagnostic tests. It is anticipated that this program will encompass Army, Air Force and Navy dependents.

PRIOR AND CURRENT PROGRESS

This HIH/HICHD funded project was begun in 1988. For the period of July 1988 through May 1989, twenty-nine children in 25 families were enrolled on study RV13, WU#6220. HIV infection has been documented in 10 patients (6 asymptomatic - P1, and 4 symptomatic/AIDS - P2). HIV infection has not yet been detected in 19 children (P0). In these families 19 mothers were HIV infected while only 9 fathers had documented HIV infection. Four other families have each enrolled 2 children. Military service status is as follows: Army - 21, Air Force - 2, Navy - 2, PHS - 2, and the Marine - 2.

CONCLUSIONS

The preliminary data suggest that HIV infection does occur in military families and that maternal infection in the absence of HIV infection in the father is common. Approximately one third of the children enrolled in this study to date have been confirmed to have HIV infection.

REPORT DATE: 10/02/89

WORK UNIT # 6222

DETAIL SUMMARY SHEET

TITLE: Core Project: Evaluation of Diagnostic Assays for Human Immunodeficiency Virus (HIV) in Children with Evidence of HIV Exposure or HIV Illnesses

KEYWORDS: AIDS, diagnosis, cultures

PRINCIPAL INVESTIGATOR: Fischer, Gerald COL MC

ASSOCIATES: Burke, Donald COL MC; Ascher, David MAJ MC

DEPARTMENT: HIV Research

STATUS: Ongoing

APPROVAL DATE: Sep 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

- a) To analyze laboratory assays for detection of HIV infection in children; and
- b) to correlate the results with the clinical status of the child.

TECHNICAL APPROACH

This protocol will evaluate the usefulness of new diagnostic assays for HIV as they are developed using blood from HIV-infected or high risk children. Blood will be sent to the laboratory for standard ("state of the art") HIV testing (generally those tests that are most developed). The surplus will be utilized for less well developed assays or stored for future analysis. Results from all tests will be compared to conventional assays used to diagnose adult HIV infection (ELISA, Western Blot) to determine their usefulness in children.

PRIOR AND CURRENT PROGRESS

We have performed 110 HIV cultures among 62 patients. Sensitivity among seropositive patients over 18 months is 97.4% and specificity is 97%. Sensitivity of culture in patients from birth to 18 months is currently 93% but is expected to decline as false negative cultures from birth are recognized. Overall 70% of cultures are positive at 7 days incubation or less. Positive cultures requiring more than 7 days incubation were exclusively associated with early clinical disease (CDC P1), while all patients with advanced disease (CDC P2) were culture positive at 7 days or less ( $P=0.0002$ ). Plasma viremia was also associated with advanced disease stage ( $P=0.002$ ).

CONCLUSIONS

HIV cultures have been exceedingly valuable in the diagnosis and staging of children with HIV infections. These studies are ongoing.

REPORT DATE: 10/20/89

WORK UNIT # 7128

DETAIL SUMMARY SHEET

TITLE: Neurobehavioral Consequences of HTLV-III Brain Infection and AIDS  
Encephalopathy

KEYWORDS: HIV, AIDS, neurobehavior

PRINCIPAL INVESTIGATOR: Salazar, Andres COL MC

DEPARTMENT: HIV Research

STATUS: Ongoing

APPROVAL DATE: Dec 1986

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To study the neurologic and behavioral effects of AIDS.

TECHNICAL APPROACH

Initial and six month follow-up multidisciplinary evaluation of Stage I, II, and III patients.

PRIOR AND CURRENT PROGRESS

To date 132 individuals have been enrolled; this includes 70 HIV+ individuals, 29 HIV seronegative normal controls, 23 HIV-controls with adjustment disorders, and 10 HIV neurologic disease controls. Of the HIV+ subjects, 50 have been reevaluated once (six-month follow-up), 34 have been reevaluated twice (6 and 12 months), and 9 three times (6, 12 and 18 months). Six normal controls have also received a 6 month reevaluation.

CONCLUSIONS

Ongoing data analyses have revealed subtle cognitive dysfunction in a subgroup of the HIV+ infected group that is not attributable to current degree of depression or anxiety. These changes are consistent with a "subcortical" dementia with slowed information processing as a prominent feature. Progressive slowing on reaction time tasks has been documented on repeat evaluations. The frequency of abnormal EEG and MRI examinations has increased over time.

REPORT DATE: 06/13/89

WORK UNIT # 7139

DETAIL SUMMARY SHEET

TITLE: Intramuscular Poly-ICLC and Zidovudine in the Management of HIV  
Infection: An Open Pilot Trial

KEYWORDS:

PRINCIPAL INVESTIGATOR: Salazar, Andres COL MC

DEPARTMENT: HIV Research

STATUS: Ongoing  
APPROVAL DATE: Jul 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine the safety or toxicity of Poly-ICLC plus Zidovudine in patients with advanced HIV infection based on historical controls. To study the human response to Poly-ICLC plus Zidovudine in patients with AIDS. To explore Zidovudine in the management of HIV Infection, based in historical controls.

TECHNICAL APPROACH

Poly-ICLC (5,10,50 or 100 mcgm/kg) is administered IM one to four times a month. Clinical, laboratory, and immunological parameters are followed.

PRIOR AND CURRENT PROGRESS

Seven patients have been entered in the study to date. All have tolerated treatments well. Accessions did not begin until February 1989.

CONCLUSIONS

Poly-ICLC can be safely administered to AIDS patients.

REPORT DATE: 03/01/89

WORK UNIT # 8801

DETAIL SUMMARY SHEET

TITLE: Identification and Characterization of Human Immunodeficiency Virus in Human Semen

KEYWORDS: HIV, semen

PRINCIPAL INVESTIGATOR: Rhoads, Joanne MAJ MC

ASSOCIATES: Anderson, Deborah

DEPARTMENT: HIV Research

STATUS: Ongoing

APPROVAL DATE: Mar 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To identify, through culture and antigen detection, HIV in human semen and to characterize the immune response to HIV in the seminal compartment.

TECHNICAL APPROACH

a) Culture of semen (cell and seminal plasma); b) Evaluation of seminal plasma for HIV antibodies with comparison to serum HIV antibodies (ELISA and Western Blot); c) Evaluation of HIV antigens in the seminal plasma (p24 ELISA).

PRIOR AND CURRENT PROGRESS

Fifteen semen specimens were cultured for HIV - 4+. Western Blots and ELISA's were done on matched semen (seminal plasma) and serum (7 pairs done) indicate differential antibody production in the two compartments, with minimum antibodies directed against the gag proteins in the seminal compartment.

CONCLUSIONS

The data to date support the concept that the male reproductive tract is an immunologically privileged site and HIV replication and control in this compartment may differ from the serum.

REPORT DATE: 03/06/89

WORK UNIT # 8802

DETAIL SUMMARY SHEET

TITLE: VA Cooperative Study No. 298, Treatment of AIDS and AIDS Related Complex; Part I: Treatment of Patients with ARC (AZT Vs. Placebo)

KEYWORDS: zidovudine, HIV, ARC

PRINCIPAL INVESTIGATOR: Oster, Charles COL MC  
ASSOCIATES: Hawks, Clifton MAJ MC

DEPARTMENT: HIV Research

STATUS: Ongoing  
APPROVAL DATE: Apr 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine the effectiveness of AZT (Zidovudine) on AIDS Related Complex (ARC) - Walter Reed Stages two through five.

TECHNICAL APPROACH

This is a randomized double-blind placebo-controlled study. Subjects who meet the inclusion criteria, after screening, are randomized onto the study drug. Half of the subjects receive (AZT) 250 mg. every four hours, while the other half receive a placebo.

PRIOR AND CURRENT PROGRESS

A total of twenty-four patients have been screened since 1 August 1988. Seventeen of these patients have met the inclusion criteria to date and have been randomized onto the study drug. Since randomization, two patients have voluntarily withdrawn from the study for personal reasons, and one patient was involuntarily withdrawn for reasons of noncompliance with medication dosage. One additional patient's dosage has been temporarily stopped due to anemia.

CONCLUSIONS

This study is ongoing, and therefore no conclusions have been reached.

REPORT DATE: 03/27/89

WORK UNIT # 8803

DETAIL SUMMARY SHEET

TITLE: Core Protocol for HIV Developmental Diagnostics (Adults)

KEYWORDS: HIV, AIDS, virus culture

PRINCIPAL INVESTIGATOR: Burke, Donald COL MC

DEPARTMENT: HIV Research

STATUS: Ongoing

APPROVAL DATE: May 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To develop and evaluate new and/or improved laboratory methods for establishing the diagnosis of HIV infection and for determining the stage of illness.

TECHNICAL APPROACH

Methods to detect replicating HIV virus, HIV antigens, and HIV nucleic acids are used, including for example virus culture, antigen capture immunoassay, and polymerase chain reaction (PCR) amplification of HIV DNA.

PRIOR AND CURRENT PROGRESS

The rate of isolation of HIV from peripheral blood mononuclear cells from HIV seropositive subjects is directly related to the stage of illness. There are between 10 and 10,000 (mean 100) infected cells per milliliter of blood. Rates of isolation from T-helper cells and from macrophages are comparable. PCR detects as few as 10 copies of HIV genome per specimen.

CONCLUSIONS

New methods such as virus culture and polymerase chain reaction can be used for detection and quantitation of HIV in clinical samples.

REPORT DATE: 04/04/89

WORK UNIT # 8804

DETAIL SUMMARY SHEET

TITLE: The Natural History of HIV Infection and Disease in United States Military Beneficiaries

KEYWORDS: HIV, natural history, AIDS

PRINCIPAL INVESTIGATOR: Oster, Charles COL MC

DEPARTMENT: HIV Research

STATUS: Ongoing  
APPROVAL DATE: May 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To systematically document the natural disease progression of HIV infection.

TECHNICAL APPROACH

Information, already being routinely collected on HIV patients, is being organized into a data base in such a way that more scientifically valid information will be forthcoming. Safeguards to patient confidentiality are met. This data base forms the core around which other specific protocols can be built.

PRIOR AND CURRENT PROGRESS

To date, 202 patients have been enrolled.

CONCLUSIONS

This study is ongoing, and therefore no conclusions have been reached.

REPORT DATE: 11/02/89

WORK UNIT # 9269

DETAIL SUMMARY SHEET

TITLE: Evaluation of Human Immunodeficiency Virus (HIV)-Related Proteins on the Surface of Lymphocytes from Patients with Evidence of HIV Exposure or HIV Illnesses

KEYWORDS: AIDS, lymphocyte, antigens

PRINCIPAL INVESTIGATOR: Baker, James MAJ MC

DEPARTMENT: HIV Research

STATUS: Terminated

APPROVAL DATE: Jun 1987

FUNDING: Current FY: \$ 384 Previous FYs: \$ 7,001 Total: \$ 7,385

STUDY OBJECTIVE

Quantify HIV infection by determining the number of HIV-positive lymphocytes.

TECHNICAL APPROACH

Use monoclonal antibodies against viral proteins in conjunction with fluorescein conjugated antibodies to stain the peripheral blood lymphocytes from HIV-infected individuals; then measure these cells using a flow cytometer.

PRIOR AND CURRENT PROGRESS

Thirty-three patients enrolled so far; most symptomatic individuals have evidence of infected, antigen positive lymphocytes while controls have not had these cells.

CONCLUSIONS

ADMINISTRATIVELY TERMINATED

REPORT DATE: 01/30/90

WORK UNIT # 3214

DETAIL SUMMARY SHEET

TITLE: In Vitro Lymphocyte Suppression by Calcium Channel Blocking Drugs

KEYWORDS: lymphocyte, calcium, calcium channel blocking

PRINCIPAL INVESTIGATOR: Birx, Deborah MAJ MC

SERVICE: Allergy/Immunology Service

STATUS: Terminated

APPROVAL DATE: Apr 1984

FUNDING: Current FY: \$ 8,538 Previous FYs: \$ 16,761 Total: \$ 25,299

STUDY OBJECTIVE

Identify the role of calcium in lymphocyte activation including early and late T cell activation and B cell activation.

TECHNICAL APPROACH

a) Isolate normal human T and B cells; b) Use different chemical probes that cause blockade in cellular calcium cascade to study their importance in cellular activation.

PRIOR AND CURRENT PROGRESS

We have identified the essential early events in lymphocyte activation as related to Ca<sup>++</sup>. These events have been studied in both T and B cells. Our current progress consists of attempts to get to recent rewritten papers published involving secondary activation and K-2 expression in both T and B cells. These papers are being rewritten for resubmission and no new experiments will be conducted until the reviewer comments are received. We have continued interest in pertussis toxin and its effect on lymphocyte activation through 6 proteins.

CONCLUSIONS

ADMINISTRATIVELY TERMINATED.

REPORT DATE: 07/18/89

WORK UNIT # 3221

DETAIL SUMMARY SHEET

TITLE: The Role of IgG Subclasses in Hymenoptera Hypersensitivity and Immunotherapy

KEYWORDS: IgG subclasses, hymenoptera, immunotherapy

PRINCIPAL INVESTIGATOR: Engler, Renata MAJ MC

ASSOCIATES: Squire, Edward LTC MC; Salata, Kalman PhD

SERVICE: Allergy/Immunology Service

STATUS: Ongoing

APPROVAL DATE: Aug 1984

FUNDING: Current FY: \$ 8,195      Previous FYs: \$ 13,332      Total: \$ 21,527

STUDY OBJECTIVE

Objectives are: Development of a Hymenoptera venom specific ELISA assay for the measurement of IgG, IgG1/2/3/4 subclasses to honey bee, wasp, yellow jacket, yellow hornet, white faced hornet. Comparison of ELISA assay with the radioimmunoassay. Comparison of venom-specific IgG and IgG-subclass levels in patients on immunotherapy versus untreated patients a history of anaphylaxis. To follow patients on immunotherapy with serial venom specific G measurements.

TECHNICAL APPROACH

Patients are enrolled in the study during the clinic's routine bee allergy evaluation days. The parameters evaluated in each patient, include: a) skin test titration with specific venoms; b) RIA testing for venom specific IgG and IgE; c) ELISA assays for venom-specific G4 and G<sub>1</sub>. VS-G and G4 levels are followed sequentially in patients on venom immunotherapy and compared to untreated patients. In addition, VS-G and G4 levels are correlated to protection from natural sting reactions and level of severity of previous sting reactions.

PRIOR AND CURRENT PROGRESS

Two hundred patients have been enrolled in the study to date. A sensitive and specific ELISA assay for the measurement of VS-G1, G4 and total G has been developed; both VS-G and G4 correlate well with a reputable commercial radioimmunoassay. A computerized database has been utilized to track patients in follow-up and correlate clinical response to Venom and VS-G/G4. Serum venom specific IgE (VS-E) is obtained through a commercial Rast Laboratory because the ELISA is not adequately sensitive. In some patients, the VS-E/G ratio, may be a better predictor of risk for Anaphylaxis prior to and during VIT, but this will require continued patient follow-up.

CONCLUSIONS

VS-G levels correlate to protection against anaphylaxis in the first 3 to 4 years of venom immunotherapy (VIT). These levels decrease after 5 years of VIT but G4 levels appear to remain elevated. G4 may be a better parameter of protection even after VIT is stopped.

REPORT DATE: 12/14/89

WORK UNIT # 3224

DETAIL SUMMARY SHEET

TITLE: Assessment of Target Organ Reactivity in Anaphylaxis

KEYWORDS: anaphylaxis, organ, reactivity

PRINCIPAL INVESTIGATOR: Smith, Laurie

SERVICE: Allergy/Immunology Service

STATUS: Ongoing

APPROVAL DATE: Jan 1985

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine if patients who exhibited chest symptoms with anaphylaxis but without a history of asthma had underlying bronchial hyperreactivity.

TECHNICAL APPROACH

Bronchial reactivity to histamine was determined by standard protocol as described by Chai in patients who had anaphylaxis with or without accompanying chest symptoms.

PRIOR AND CURRENT PROGRESS

Currently no work is being done in protocol because there is no fellow interested in this protocol.

CONCLUSIONS

We would like to hold this protocol as open but inactive for now. If no fellow picks it up next year we will retire it.

REPORT DATE: 12/06/89

WORK UNIT # 3225

DETAIL SUMMARY SHEET

TITLE: Development of Human Hybridoma IgE Antibodies for Use in Clinical Applications

KEYWORDS: IgE, hybridoma, human

PRINCIPAL INVESTIGATOR: Baker, James MAJ MC

SERVICE: Allergy/Immunology Service

STATUS: Terminated

APPROVAL DATE: Nov 1985

FUNDING: Current FY: \$ 1,430 Previous FYs: \$ 0 Total: \$ 1,430

STUDY OBJECTIVE

Development of human hybridoma IgE antibodies for use in clinical application.

TECHNICAL APPROACH

To develop human hybridoma antibodies using newly available fusion techniques including HMMA 2.11 TG/O fusion partner (a human mouse heteromycloma) and lymphokines IL-4 and IL-6.

PRIOR AND CURRENT PROGRESS

Previous studies using human fusion partner SHM-D33 and EBV transformed lymphocytes were unsuccessful. The new fusion partner has been shown to have such a high fusion rate that it can be used for direct fusion of peripheral cells. These cells will be treated with lymphokines which have recently been shown to favor IgE production. These two advances dramatically increase the probability for success of this protocol.

CONCLUSIONS

ADMINISTRATIVELY TERMINATED.

REPORT DATE: 12/06/89

WORK UNIT # 3229

DETAIL SUMMARY SHEET

TITLE: Delayed-type Hypersensitivity Skin Testing: Correlation with Skin Biopsy and In Vitro Lymphocyte Testing in Normal Volunteers.

KEYWORDS: DTH, delayed-type, hypersensitivity

PRINCIPAL INVESTIGATOR: Squire, Edward LTC MC

SERVICE: Allergy/Immunology Service

STATUS: Ongoing

APPROVAL DATE: Aug 1986

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

Identify frequency of false positive and false negative delayed-type skin tests using skin biopsy as the definitive test.

TECHNICAL APPROACH

Fifty normal subjects were studied by a) applying DTH skin tests; 48 degrees later measure the maximum extent of erythema and induration; b) biopsy of all candida and tetanus skin test 3 mm punch bx and pathologic renew; c) performing in vitro lymphocyte response to tetanus and candida in quadruplicate; d) a serial dilutions and score responsiveness.

PRIOR AND CURRENT PROGRESS

The principal investigator has moved permanently. While this protocol is inactive at present, we would like to maintain it as the study promises to be an important area for continuing work. Should another fellow-in-training be interested in pursuing it.

CONCLUSIONS

Request that study remain open.

REPORT DATE: 02/16/89

WORK UNIT # 3330

DETAIL SUMMARY SHEET

TITLE: Skin Testing for Anergy and Quality of Candida Extracts

KEYWORDS: DTH, delayed-type, skin test

PRINCIPAL INVESTIGATOR: Squire, Edward LTC MC

SERVICE: Allergy/Immunology Service

STATUS: Ongoing

APPROVAL DATE: Mar 1986

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

Evaluate the bioequivalency of Candida and Trichophyton extracts used for delayed-type hypersensitivity skin testing.

TECHNICAL APPROACH

1) Comparison of 6 Candida products and 9 Trichophyton products. 2) DTH skin tests to normal volunteers; in vitro analysis with isoelectric focusing and laser densitometry.

PRIOR AND CURRENT PROGRESS

Candida and Trychophyton extracts available commercially do not represent bioequivalent products. A method of standardization to bioequivalence is sorely needed. Results for Candida will be published in JAMA LE8334, results for Trychophycton are being submitted to JAMA.

CONCLUSIONS

REPORT DATE: 08/11/89

WORK UNIT # 3335

DETAIL SUMMARY SHEET

TITLE: Do Aeroallergens Exacerbate Atopic Dermatitis

KEYWORDS: aeroallergens

PRINCIPAL INVESTIGATOR: Squire, Edward LTC MC

SERVICE: Allergy/Immunology Service

STATUS: Completed  
APPROVAL DATE: Sep 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

Determine if Atopic Dermatitis is exacerbated by airborn allergens.

TECHNICAL APPROACH

Phase I. Identification of patients with atopic dermatitis possibly exacerbated by airborn allergens. Phase II. Performance of a controlled challenge which simulates natural exposure.

PRIOR AND CURRENT PROGRESS

No patients enrolled. It is the PI's decision to close the protocol due to it's inactivity and the priority status of other active studies.

CONCLUSIONS

Study closed.

REPORT DATE: 10/13/88

WORK UNIT # 3336

DETAIL SUMMARY SHEET

TITLE: The Effect of Human Breast Milk Cell Supernatants on In Vitro Immunoglobulin Secretion

KEYWORDS:

PRINCIPAL INVESTIGATOR: Yang, Edward MAJ MC

SERVICE: Allergy/Immunology Service

STATUS: Ongoing

APPROVAL DATE: Nov 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

It is the purpose of this study to determine the effect of human breast milk cell supernatants on the immunoglobulin production of normal human peripheral blood lymphocytes.

TECHNICAL APPROACH

Using previously described cell culture techniques, human breast milk cells are harvested and placed in culture for 7 days and the supernatants (BMCS) are harvested for assay. Peripheral blood lymphocytes (PBL) are cultured with BMCS and a series of mitogen. Immunoglobulin secretion is assessed utilizing ELISA system.

PRIOR AND CURRENT PROGRESS

Since final approval of the protocol, three subjects have been enrolled in the breast milk collection part of the study. Three 2 week samples and one colostrum sample have been harvested. A series of experiments have been performed in order to standardize the assay system. Preliminary data suggests that breast milk cells selectively secrete IgA and induce PBL's to secrete IgA. Standardization of the assays to establish reproducibility of the data is in progress.

CONCLUSIONS

The mucosal immune response of the breast results in profound IgA secretion which persists when breast milk cells are placed in culture after washing. The mechanism of this isotype switching remains unclear but a cytokine produced by BMC's may be responsible for this Ig response.

REPORT DATE: 12/28/89

WORK UNIT # 3337

DETAIL SUMMARY SHEET

TITLE: What is the Dose Response to Ipratropium Bromide (IB) Among Steroid Dependent Asthmatics?

KEYWORDS: ipratropium bromide, steroid dependent asthma, dose response

PRINCIPAL INVESTIGATOR: Squire, Edward LTC MC

SERVICE: Allergy/Immunology Service

STATUS: Completed

APPROVAL DATE: Feb 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine whether ipratropium bromide is likely to be useful in the management of severe asthma.

TECHNICAL APPROACH

Doubleblind, placebo controlled dose study.

PRIOR AND CURRENT PROGRESS

Four patients enrolled.

CONCLUSIONS

Ipratropium unlikely to contribute to clinical benefit of asthmatics.

REPORT DATE: 12/28/89

WORK UNIT # 3338

DETAIL SUMMARY SHEET

TITLE: Comparison of Skin Test Reactivity to Dilutions of Histamine Using the Volar Surface of the Arm Vs. the Back

KEYWORDS: epicutaneous, skin tests, histamine

PRINCIPAL INVESTIGATOR: Herrera, Alma MAJ MC

SERVICE: Allergy/Immunology Service

STATUS: Completed  
APPROVAL DATE: Mar 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

Determine skin test reactivity forearms versus back.

TECHNICAL APPROACH

Comparison of reactivity to three dilution of histamine.

PRIOR AND CURRENT PROGRESS

Forty-one patients evaluated.

CONCLUSIONS

No difference that are likely to be clinically relevant.

REPORT DATE: 06/16/89

WORK UNIT # 3339

DETAIL SUMMARY SHEET

TITLE: Comparison of House Dust Mite Educational Programs on Selected Outcome Variables

KEYWORDS: house dust mites, D.farinae, D.pteronyxinus

PRINCIPAL INVESTIGATOR: Squire, Edward LTC MC

ASSOCIATES: Huss, Karen; Salata, Kalman PhD; Carpenter, Gary

SERVICE: Allergy/Immunology Service

STATUS: Ongoing

APPROVAL DATE: Jul 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

Does a computerized education program about avoidance measures for house dust mite antigen lead to reduced exposure in patients with asthma?

TECHNICAL APPROACH

This is a randomized trial. Fifty-two patients were followed with symptom diaries and home visits to determine to what extent environmental measures were taken in response to practitioner's recommendation. Dust samples were collected from each home and assayed for relevant dust mite allergens, both before and after patient instructions.

PRIOR AND CURRENT PROGRESS

Patient enrollment, specimen collection, and data collection are complete. Data analysis is ongoing.

CONCLUSIONS

Deferred pending the completion of data analysis.

REPORT DATE: 09/29/89

WORK UNIT # 3340

DETAIL SUMMARY SHEET

TITLE: Analysis of Carbohydrate Epitopes on Food Allergen Proteins: A Pilot Study

KEYWORDS: carbohydrate, epitopes, allergens

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD

ASSOCIATES: Birx, Deborah MAJ MC; Engler, Renata LTC MC

SERVICE: Allergy/Immunology Service

STATUS: Ongoing

APPROVAL DATE: Aug 1988

FUNDING: Current FY: \$ 5,606 Previous FYs: \$ 0 Total: \$ 5,606

STUDY OBJECTIVE

The object of this pilot study is to identify and characterize carbohydrate epitopes on food allergens which react with specific IgE of patients with food allergy.

TECHNICAL APPROACH

Fluorescent enzyme linked immunosorbant assays (FELISA), sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE), isoelectric focusing (IEF), and immunoblotting are used to examine the role of carbohydrate epitopes in food allergy. Glycosidases, lectins and purified saccharides are used to identify carbohydrate epitopes recognized by specific IgE from patients with food allergy.

PRIOR AND CURRENT PROGRESS

Methods have been developed to analyze food allergens using SDS-PAGE, IEF, immunoblotting, FELISA, and FELISA inhibition. A total of 9 subjects have been enrolled, 7 food allergic subjects and 2 normal subjects. Blocking IgG does not appear to be a problem. There were no adverse reactions, no patients withdrew, and there was no benefit to the patients.

CONCLUSIONS

A number of methods have been developed to measure specific IgE to food allergens. So far these methods appear to work well with samples from patients with high levels of specific IgE. Blocking IgG does not appear to be a problem. Carbohydrate analyses will be carried out with serum samples from patients with high levels of specific IgE. These are, generally, patients with the most serious disease.

REPORT DATE: 06/19/89

WORK UNIT # 3341

DETAIL SUMMARY SHEET

TITLE: Occurrence of Laryngeal Dysfunction Among Patients Initially Diagnosed as Having Bronchial Asthma

KEYWORDS: asthma, laryngeal dysfunction, laryngeal dyskinesis

PRINCIPAL INVESTIGATOR: Squire, Edward LTC MC

ASSOCIATES: Moyer, Joseph MAJ MC

SERVICE: Allergy/Immunology Service

STATUS: Ongoing

APPROVAL DATE: Aug 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

a) Define a standard approach to the evaluation of patients with suspected laryngeal dysfunction; b) Define the frequency of laryngeal dysfunction occurring with and without bronchial asthma among active duty military.

TECHNICAL APPROACH

a) Evaluate patients specifically identified as probably having laryngeal dysfunction; b) Comprehensively evaluate active duty soldiers at Walter Reed who have a profile or seek medical attention for exercise related lung symptoms.

PRIOR AND CURRENT PROGRESS

A cooperative relationship and agreed upon approach has been established between the Allergy/Immunology Service and Pulmonary Service. This approach has lead to definitive workups for five patients.

CONCLUSIONS

The existing workup, which includes rhinolaryngoscopy with a video record has confirmed the diagnosis of patients with presumptive laryngeal dysfunction. What continues to be unclear, is the actual prevalence of this disorder and the frequency with which it co-exists with asthma.

REPORT DATE: 03/16/89

WORK UNIT # 9027

DETAIL SUMMARY SHEET

TITLE: Prevalence of Antibiotic Associated Colitis among Patients on Prolonged Antibiotic Therapy

KEYWORDS: antibiotic colitis, ELISA, clostridium

PRINCIPAL INVESTIGATOR: Dobek, Arthur PhD

ASSOCIATES: Rothman, Sara PhD

DEPARTMENT: Department of Clinical Investigation

STATUS: Ongoing

APPROVAL DATE: Mar 1981

FUNDING: Current FY: \$10,502 Previous FYs: \$ 22,744 Total: \$ 33,246

STUDY OBJECTIVE

To compare the sensitivity and specificity of routine versus research diagnostic test(s) in determining the presence of Clostridium difficile toxins A and B found in stool specimens from patients with antibiotic-associated colitis.

TECHNICAL APPROACH

Our current procedure involves the analysis of the activity of mouse monoclonal IgM as a primary antibody in an ELISA (modified from the procedure of L.A. Magnarelli, J. Clin. Microbiol. 20: 181-184 (1984) in which the antigen is either C. difficile toxin A or B. Additional experiments involving a competitive ELISA procedure were performed using alkaline phosphatase conjugated a secondary antibody to various mouse monoclonal IgM antibodies. A semi-automated ELISA procedure was tested using the modified Magnarelli method. We have recently analyzed the serum from normal, toxoid A- and toxoid B-immunized guinea pigs to determine the presence or absence of toxin specific IgG antibodies.

PRIOR AND CURRENT PROGRESS

Our ELISA procedure was adapted to detect the binding of guinea pig polyclonal antibodies. After 25 guinea pigs were immunized with either toxoid A or B, A and B, or saline, the sera IgG antibody binding ability to the respective purified toxons was determined. Most sera reacted strongly with the homologous antigens, but there were a few sera with a slight cross reactivity to the heterologous toxins. Sera from those animals receiving both toxoids generally reacted only with toxin A. This suggests a lowered immune response to toxoid B when toxoid A is injected with it. Sera from saline controls showed little or no binding to either toxin.

CONCLUSIONS

Whereas previous ELISA studies have yielded specific reactions between toxins A and B versus mouse IgM antibodies, we can now add a similar specific reaction with guinea pig serum IgG antibodies against these same toxins. Thus, our ELISA procedure is specific in another animal system with its IgG. The potential for success with our ELISA methods using human antisera may also be achievable and should be considered.

REPORT DATE: 06/20/89

WORK UNIT # 9255

DETAIL SUMMARY SHEET

TITLE: Evaluation of DIGDOS, an HP-85 Program to Assist in Digoxin Dosing Decisions

KEYWORDS: digoxin, drug levels, clearance

PRINCIPAL INVESTIGATOR: Schuster, Brian LTC MC

ASSOCIATES: Harder, John MD

DEPARTMENT: Department of Clinical Investigation

STATUS: Ongoing

APPROVAL DATE: Oct 1983

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To evaluate the suitability for dosing projections of digoxin population pharmacokinetic parameters from the literature for WRAMC patients.

TECHNICAL APPROACH

Record review of charts of patients who had two or more serum digoxin levels. Bayesian analysis with HP-85 program to test initial estimates and ability to predict second (or last if more than two) serum digoxin level.

PRIOR AND CURRENT PROGRESS

Following initial evaluation of 31 WRAH patients (Harter et al, ASCPT xx:yy, 198z) which showed published NONMEM CL did not correct for WRAH patients, an additional 29 patients were added from NDA data. The 60 combined patients were analyzed by NONMEM and DIGDOS. The results were similar to the original WRAH patient findings, suggesting a problem with using a one compartment NONMEM model with routine digoxin plasma samples (all drawn after 6 hours).

CONCLUSIONS

Published values for digoxin clearance are probably in error and should be multiplied by 1.5. The reason for the problem with NONMEM should be pursued in order to better understand both NONMEM and digoxin pharmacokinetics.

REPORT DATE: 11/02/89

WORK UNIT # 9261

DETAIL SUMMARY SHEET

TITLE: Development of Human Hybridomas for Use in Histocompatibility Testing

KEYWORDS: hybridomas, histocompatibility, monoclonal antibody

PRINCIPAL INVESTIGATOR: Baker, James MAJ MC

DEPARTMENT: Department of Clinical Investigation

STATUS: Terminated

APPROVAL DATE: Aug 1985

FUNDING: Current FY: \$23,904 Previous FYs: \$ 76,008 Total: \$ 99,912

STUDY OBJECTIVE

To isolate lymphocytes producing antibodies to specific HLA class I or II determinants from patients stimulated by renal allograft rejection. These antibodies would then be used to more accurately define the HLA type in histocompatibility testing as compared to the historical method using polyclonal antisera from multiporous women or even recently developed methods utilizing mouse monoclonal antibodies.

TECHNICAL APPROACH

Lymphocytes are purified from 25-30 cc blood obtained from patients with-titered HLA antibody and are transformed in vitro with Epstein Barr Virus. These cells are cultured at approximately  $2 \times 10^5$  cells/well in 24 well plates, incubated and fed until they have grown to a visible concentration. They are then screened for potential HLA specific antibody production, and positive cell lines are grown up, recloned and fused to heteromyeloma cell line SHM-D33. Viable cells are then retested, cloned five times, and the antibody characterized.

PRIOR AND CURRENT PROGRESS

Due to increased cases of HIV and continuing misunderstandings of AIDS among transplant patients, there is great reluctance to volunteer for blood donations beyond those necessary to evaluate their status as patients. Of the 20-25 patients interviewed, none chose to participate in the protocol. A new fusion partner for future work has been identified (MMMA 2.11 TG/O) and will be received in the next week. Its reported fusion rate and the stability of fusions should greatly increase our ability to isolate and perpetuate antibody-producing lymphocytes of interest. Two other fusion partners tested proved to be less satisfactory than SHM.D33.

CONCLUSIONS

Better education of the patients is necessary to reassure them that blood donations will not expose them to HIV. Work should continue on the new fusion partner to provide optimum conditions for developing the monoclonal antibody producing lymphocyte of interest. ADMINISTRATIVELY TERMINATED.

REPORT DATE: 10/06/88

WORK UNIT # 9262

DETAIL SUMMARY SHEET

TITLE: Internalization and Cellular Processing of 125-I-Epidermal Growth Factor (EGF) in Responsive and Unresponsive Cell Lines

KEYWORDS: growth factors, processing, DNA synthesis

PRINCIPAL INVESTIGATOR: Schaudies, Paul CPT MS

ASSOCIATES: Wray, Linton COL MC

DEPARTMENT: Department of Clinical Investigation

STATUS: Completed

APPROVAL DATE: Oct 1985

FUNDING: Current FY: \$ 8,926 Previous FYs: \$ 98,554 Total: \$ 107,480

STUDY OBJECTIVE

To determine mechanism by which cells respond to mitogenic growth stimulus.  
Study biological role of EGF in the rat model.

TECHNICAL APPROACH

Compare and contrast epidermal growth factor (EGF) stimulated/mediated events in cells which vary in their growth responsiveness to EGF. Study the effects of EGF in the gastro intestinal tract of developing and adult rats in order to establish a biological role for the growth factor.

PRIOR AND CURRENT PROGRESS

1) Established different patterns of EGF processing in responsive and nonresponsive human fibroblasts. 2) Established EGF levels in gastrointestinal tract of adult and suckling rats along with the effects of fasting and treatment with cortisone and T3. 3) Quantitated immunoreactive EGF levels in rat milk and identified an EGF precursor in milk. 4) Quantitated and characterized EGF immunoreactive material in isolated regions of the rat brain.

CONCLUSIONS

1) Processing of EGF correlates with responsiveness of all line. 2) Gastrointestinal EGF levels are dependent on dietary intake. 3) Precursor to EGF in rat milk is converted by tryptic digestion. 4) Multiple forms of immunoreactive EGF waste in rat brain.

REPORT DATE: 11/08/88

WORK UNIT # 9263

DETAIL SUMMARY SHEET

TITLE: Neurohumoral Regulation of Ventilation in Patients with Elevated Adrenocorticotropic Hormone (ACTH) and Beta Endorphins (BE)

KEYWORDS: beta endorphine, CRH, respiratory control

PRINCIPAL INVESTIGATOR: Derderian, Sarkis LTC MC

DEPARTMENT: Department of Clinical Investigation

STATUS: Ongoing

APPROVAL DATE: Oct 1985

FUNDING: Current FY: \$ 864 Previous FYs: \$ 0 Total: \$ 864

STUDY OBJECTIVE

Examine the role of B-endorphine and other neuopeptides in the regulation of respiration.

TECHNICAL APPROACH

To noninvasively assess respiratory function while hypeapnic rebreathing in patients with Addison's disease. Assessments are being performed after the administration of naloxone, placebo or dexamethasone.

PRIOR AND CURRENT PROGRESS

We have studied only six patients to date. The naloxone data is inconclusive. Patients have generally been demonstrated to have a blunted carbone dioxide response and this response is further blunted after administering and dexamethasone.

CONCLUSIONS

The number of subjects is small but preliminary results suggest a role for CRF in the regulation of respiration.

REPORT DATE: 11/15/89

WORK UNIT # 9266

DETAIL SUMMARY SHEET

TITLE: The Treatment of Graves' Disease with Anti-Idiotype Therapy Using Intravenous Immunoglobulin

KEYWORDS: Graves' disease, anti-idiotype, IV immunoglobulin

PRINCIPAL INVESTIGATOR: Baker, James MAJ MC

ASSOCIATES: Burman, Kenneth LTC MC; Wartofsky, Leonard COL MC

DEPARTMENT: Department of Clinical Investigation

STATUS: Ongoing

APPROVAL DATE: May 1986

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

This therapy would be aimed at turning off the immune response to the thyroid gland using Anti-Idiotype Therapy. This study represents and attempt to bind TSH receptor antibodies by the use of an anti-idiotypic antisera.

TECHNICAL APPROACH

Involve the infusion of Intravenous Immunoglobulin roughly 4 gms per kilograms patient weighted over three days continuous infusion IV. Before, during and after the infusion, serum thyroid hormone parameters, as well as TSI, TBII and Immunoglobulin levels will be measured.

PRIOR AND CURRENT PROGRESS

We have performed this study on three patients; one of them did not feel well during the infusion but the others did well. We are analyzing the data now; some of the thyroid parameters are ready to now send for analysis. Dr. Baker has left the Army and I will be the PI on this important Study, Dr. Baker has the files and consent forms on the first patients but all future patients will be counseled by me and appropriate files maintained by me now that I am the PI.

CONCLUSIONS

None yet.

REPORT DATE: 09/18/89

WORK UNIT # 9267

DETAIL SUMMARY SHEET

TITLE: The Effect of Intervention Strategies on Weight Loss and Other Related Indicators in Overweight Personnel Enrolled in the Army Weight Control Program

KEYWORDS: obesity, weight control, AWCP

PRINCIPAL INVESTIGATOR: Coffey, Laurie CPT

ASSOCIATES: Rinke, Wolf PhD; Johnson, Karen CPT

DEPARTMENT: Department of Clinical Investigation

STATUS: Completed

APPROVAL DATE: Sep 1986

FUNDING: Current FY: \$ 577 Previous FYs: \$ 0 Total: \$ 577

STUDY OBJECTIVE

To determine if the type and length of an education program affects changes in body weight, percent body fat and other selected indicators.

TECHNICAL APPROACH

We are testing the effectiveness of three different intervention strategies using the following null hypothesis: There are no significant differences among soldiers who exceed the AWCP body fat standards and are enrolled in one of three intervention groups, as assessed by the following indicators: a. Body weight, b. Percent body fat, c. Army Health Risk Profile Score, d. Aerobic fitness score, e. Nutrient analysis, f. Life style assessment score.

PRIOR AND CURRENT PROGRESS

After a six month study period, changes in weight, percent body fat determined circumference technique, responses to the Army health risk profile, nutrient content of 24-hour dietary recalls, and responses to a lifestyle questionnaire were determined for 45 subjects (8 female, 37 male). Pre- and posttest data were compared using ANOVA.

CONCLUSIONS

There was no significant difference between groups for any of the parameters measured. For each group, there was no significant difference in any of the parameters measured from pretest to posttest except for responses to section 1, Nutrition and section, Exercise, and total for the lifestyle assessment questionnaire. Based on results, it doesn't matter which of 3 types of intervention is used, knowledge and attitude may change but weight loss/body fat are minimally affected.

REPORT DATE: 07/13/89

WORK UNIT # 9268

DETAIL SUMMARY SHEET

TITLE: Pulmonary Function in Patients with Arthritis Associated with Inflammatory Bowel Disease

KEYWORDS: pulmonary function, arthritis, bowel disease

PRINCIPAL INVESTIGATOR: Derderian, Sarkis LTC MC

DEPARTMENT: Department of Clinical Investigation

STATUS: Ongoing

APPROVAL DATE: May 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

Evaluate pulmonary function in patients with inflammatory bowel disease (IBD) with arthritis and compare them to patients with IBD without arthritis.

TECHNICAL APPROACH

Using full pulmonary function tests (PFTs) to include ABG's and compliance studies we plan to compare the above two groups with regard to their respiratory function.

PRIOR AND CURRENT PROGRESS

Protocol has not been initiated because of inability to recruit subjects.

CONCLUSIONS

None to date.

REPORT DATE: 06/22/89

WORK UNIT # 9270

DETAIL SUMMARY SHEET

TITLE: Incidence of Bulimia in a Selected United States Army Population

KEYWORDS: bulimia, Army, nutrition

PRINCIPAL INVESTIGATOR: Rinke, Wolf LTC SP

ASSOCIATES: Dillon, Teresa CPT SP

DEPARTMENT: Department of Clinical Investigation

STATUS: Completed

APPROVAL DATE: Aug 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

a) To examine the incidence of bulimia in U.S. Army population; b) To examine the correlation of the incidence of bulimia in the selected U.S. Army population with the individual soldier's reported attempts to meet the Army's mandated weight standards.

TECHNICAL APPROACH

The research approach used was a non-experimental design in a field type setting. A descriptive survey consisting of a 26 item questionnaire was administered to active duty Fort Meade soldiers.

PRIOR AND CURRENT PROGRESS

Five hundred and twenty-two active duty soldiers from nine different units at Fort Meade, Maryland completed the survey in the fall of 1987. The results were analyzed using descriptive survey statistics. These results were reported by the associate investigator at the University of Maryland.

CONCLUSIONS

Five individuals (1.2 percent) of the survey population met all of the criteria for bulimia. Of the six bulimics five were male and one was female. In the survey population 25.2 percent of the males and 26.4 percent of the females reported binge eating. There does not appear to be a direct link between the Army Weight Control Program and bulimia.

REPORT DATE: 09/18/89

WORK UNIT # 9271

DETAIL SUMMARY SHEET

TITLE: The Ventilatory Response to Carbon Dioxide in Compensated Hepatic Cirrhosis

KEYWORDS: GABA, respiratory control, cirrhosis

PRINCIPAL INVESTIGATOR: Derderian, Sarkis LTC MC

DEPARTMENT: Department of Clinical Investigation

STATUS: Ongoing

APPROVAL DATE: Sep 1987

FUNDING: Current FY: \$ 542 Previous FYs: \$ 8,008 Total: \$ 8,550

STUDY OBJECTIVE

To examine the potential role for Gamma Amino Butyric Acid (GABA) in the regulation of respiration.

TECHNICAL APPROACH

To non-invasively assess respiratory function and the pattern of breathing while hypercapnic rebreathing in subjects with cirrhosis of the liver and normal controls.

PRIOR AND CURRENT PROGRESS

We have completed studying 6 subjects and found that the ventilatory response to rebreathing carbon dioxide was blunted. From this we hypothesized that this may be related to the effects of GABA. We have now submitted an addendum to study additional subjects and correlate peripheral levels of this amino acid with the ventilatory response. Because of delays due to programming requirements this study has not been initiated.

CONCLUSIONS

The ventilatory response to rebreathing of carbon dioxide is reduced in patients with cirrhosis.

REPORT DATE: 08/08/89

WORK UNIT # 9272

DETAIL SUMMARY SHEET

TITLE: Relationship of Major Histocompatibility Complex Class II Genes to Inhibitor Antibody Formation in Hemophilia A

KEYWORDS: inhibitor, hemophilia A, histocompatibility

PRINCIPAL INVESTIGATOR: Lippert, Lloyd LTC MS

ASSOCIATES: Fisher, Lyman MD PhD

DEPARTMENT: Department of Clinical Investigation

STATUS: Ongoing

APPROVAL DATE: Sep 1988

FUNDING: Current FY: \$29,024 Previous FYs: \$ 0 Total: \$ 29,024

STUDY OBJECTIVE

The goal of this research is to identify a marker or trait which will prospectively identify the Hemophilia A subpopulation at risk for developing ant-factor VII inhibitor antibodies and to substantiate a statistical association between the inhibitor phenotype and the major histocompatibility complex (MHC).

TECHNICAL APPROACH

HLA phenotypes will be determined by microlymphocytotoxicity. Restriction fragment length polymorphism (RFLP) analysis is performed on peripheral blood DNA that is digested with a battery of restriction enzymes, Southern blotted and probed with class II MHC alpha and beta gene probes.

PRIOR AND CURRENT PROGRESS

Twenty-four patient specimens have been accessioned; HLA phenotyping has completed on eighteen and DNA harvested from all twenty-four.

CONCLUSIONS

Insufficient number of patients accessed to initiate complete data analysis. However, there appears to be an unexplained increased frequency of HLA-A9.

REPORT DATE: 01/03/90

WORK UNIT # 9273

DETAIL SUMMARY SHEET

TITLE: Identification and Characterization of Thyroid Autoantigens

KEYWORDS: thyroid, antigens, viral

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC

DEPARTMENT: Department of Clinical Investigation

STATUS: Ongoing

APPROVAL DATE: Sep 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

The purpose of this study is to identify antigens to which antibodies are directed in the serum and thyroid glands of patients with autoimmune thyroid disease.

TECHNICAL APPROACH

Various immunologic and molecular biologic tools are used to include chromatography of thyroid memberand, EB virus B cell immortalization, and screening clones of B cells with ELISA assays. Both T and B cells and their relevant antigens will be characterized and, further, the antigens will be sequenced and their protein structure identified.

PRIOR AND CURRENT PROGRESS

We have performed the studies mentioned above and have observed that there is a class of antigens that are relevant to the disease which seem to be histone in nature. Efforts to sequence these proteins is ongoing. Also, we have preliminary evidence that an HIV related virus may be found in thyroid or lymphocyte samples.

CONCLUSIONS

Autoimmune thyroid disease is associated with the development of multiple classes of autoantibodies directed against many different antigens. One group of these relevant antigens is histone in character. Viruses may be important in thyroid disease.

REPORT DATE: 03/20/89

WORK UNIT # 9409

DETAIL SUMMARY SHEET

TITLE: The Evaluation of 0.12% Chlorhexidine Rinse on the Prevention of Alveolar Osteitis

KEYWORDS: chlorhexidine, alveolar osteitis

PRINCIPAL INVESTIGATOR: Ragno, James MAJ DC

SERVICE: Dental Clinic

STATUS: Ongoing

APPROVAL DATE: May 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To evaluate the incidence of alveolar osteitis in third molar exodontia using standard surgical techniques. To evaluate the effectiveness of 0.12% chlorhexidine in the prevention of alveolar osteitis.

TECHNICAL APPROACH

Patients are selected and placed into one of six risk groups in a random, double blind fashion. They receive a prescribed rinse and prior to the removal of their wisdom teeth, rinse with 15 cc for 30 seconds. Teeth are removed in a standard surgical fashion and sockets are rinsed after surgery. The patient will then rinse twice a day for 6 more days and will be seen for follow-up on postop day 3 and 7. Alveolar osteitis or any other problems will be noted and treated.

PRIOR AND CURRENT PROGRESS

Seventy-three patients have been tested to date with no adverse reactions directly related to drugs investigated. No benefits can be determined as of yet due to the set up of the study as a double blind investigation. The goal is to have eighty patients done by 1 April 1989 at which time the study will be unblinded and the results tabulated.

CONCLUSIONS

None.

REPORT DATE: 10/12/88

WORK UNIT # 1516-84

DETAIL SUMMARY SHEET

TITLE: CALGB 8364: Immunological Diagnostic Studies in Adult ALL

KEYWORDS: immunology, adult ALL, leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Cancer & Leukemia Group B

APPROVAL DATE: Oct 1983

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine the incidence of various monoclonal antibodies cytochemical, and conventional lymphoid markers in adult ALL. To correlate the presence of the various markers with the initial and subsequent clinical characteristics of the disease, response rate, and response duration. To determine if marker status changes at relapse.

TECHNICAL APPROACH

Non-randomized study in which all eligible patients being entered on the ALL treatment protocol agree to allow prior to the initiation of therapy the submission of 6 air-dried unstained BM smears for confirmatory cytochemical studies and 2 cc of bone marrow aspirate along with 7 cc of peripheral blood to a designated CALGB reference laboratory. The same set of samples is again obtained at relapse.

PRIOR AND CURRENT PROGRESS

Study has been open since October 1983. To date a total of 13 patients have been entered here at WRAMC. Study accrues patients at the same rate as those protocols involved with leukemia treatment in about two per year.

CONCLUSIONS

Immunology samples are sent to a CALGB reference laboratory. Data are being studied now.

REPORT DATE: 08/28/89

WORK UNIT # 1522-84

DETAIL SUMMARY SHEET

TITLE: CALGB 8461: Cytogenetic Studies in Acute Leukemia: A Companion to CALGB 8011, 8323, 8321, and 8411

KEYWORDS: cytogenetics, acute leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Cancer & Leukemia Group B

APPROVAL DATE: Sep 1984

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine the incidence of specific chromosome abnormalities in adult Acute Non Lymphatic Leukemia (ANLL) and Acute Lymphatic Leukemia (ALL).

TECHNICAL APPROACH

All eligible patients are registered to this companion to treatment protocols. A specimen of marrow and blood is obtained at diagnosis and again at relapse.

PRIOR AND CURRENT PROGRESS

Study is still open to accrual. To date a total of 52 patients with Acute Myelogenous Leukemia (AML), ALL, or Chronic Myelogeneous Leukemia (CML) have been entered.

CONCLUSIONS

Data continues to be entered. No final conclusions to date. Material periodically updated by PI.

REPORT DATE: 12/27/89

WORK UNIT # 1527-85

DETAIL SUMMARY SHEET

TITLE: CALGB 8591: A Phase III Study of Combining Chemotherapy with Surgery and Radiotherapy for Resectable Squamous Cell Carcinoma of the Head and Neck

KEYWORDS: chemotherapy, head and neck cancer, radiotherapy

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Ongoing  
APPROVAL DATE: Feb 1985

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To test whether the addition of chemotherapy to surgery and radiotherapy prolongs disease-free survival and survival between the two study groups. To determine if the patterns of failure have been changed with the addition of chemotherapy.

TECHNICAL APPROACH

Randomized study in which all eligible patients are registered, surgerized, then randomly assigned to receive radiotherapy alone or chemotherapy followed by radiotherapy.

PRIOR AND CURRENT PROGRESS

No further progress this year although study is still open. A total of 11 patients have been entered. Of those 11 patients that were registered, only 6 went on to be randomized following surgery. Three of 11 patients did not have tumor free margin after surgery and were ineligible for randomization. One patient refused to be randomized, and 1 patient was randomized but refused chemotherapy.

CONCLUSIONS

None. Data too sparse at this time.

REPORT DATE: 02/22/89

WORK UNIT # 1528-85

DETAIL SUMMARY SHEET

TITLE: CALGB 8541: Adjuvant CAF for Pathologic Stage II Node Positive Breast Cancer: A Comparison of Three Dose Regimens

KEYWORDS: adjuvant therapy, breast cancer

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine

SERVICE: Cancer & Leukemia Group B

STATUS: Ongoing

APPROVAL DATE: Mar 1985

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine whether there is a dose-dependent relationship between disease-free survival and amount of drug administered for patients with Stage II breast cancer treated with CAF.

TECHNICAL APPROACH

Randomized study in which all eligible patients receive Cytoxan, Adriamycin, and 5 FU at one of 3 different dose levels. Low dose at 300, 30, and 300. Standard dose at 400, 40, and 400, or high dose at 600, 60, and 600mg/m<sup>2</sup> on day 1 and day 8 for 4 monthly cycles.

PRIOR AND CURRENT PROGRESS

Five additional patients were entered. To date 39 patients are enrolled. The study is still open to accrual.

CONCLUSIONS

Nodal status and tumor size are prognostic factors.

REPORT DATE: 04/11/89

WORK UNIT # 1536-85

DETAIL SUMMARY SHEET

TITLE: CALGB 8582: A Comparison of Pentostatin and Alpha Interferon in Splenectomized Patients with Active Hairy Cell Leukemia

KEYWORDS: pentostatin, alpha interferon, hairy cell leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Ongoing  
APPROVAL DATE: May 1985

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

a) To compare the frequency of response between pentostatin and alpha interferon treatment in patients with hairy cell leukemia who following splenectomy manifest active or progressive disease; b) to compare time to response between these 2 treatments; c) to compare the response duration of these 2 treatments.

TECHNICAL APPROACH

Randomized study in which patients receive either Alpha interferon or pentostatin for 3 months. Patients are then assessed and continued on the same therapy or switched to the opposite therapy.

PRIOR AND CURRENT PROGRESS

Study has been open since February 1989. To date only one patient has been entered. That patient progressed while on study and has since expired.

CONCLUSIONS

None; data too sparse.

REPORT DATE: 08/27/89

WORK UNIT # 1539-85

DETAIL SUMMARY SHEET

TITLE: CALGB 8561: Retrospective Assessment of Psychosocial Sequelae in Long-term Survivors of Advanced Hodgkin's Disease

KEYWORDS: psychosocial, Hodgkin's disease

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Completed  
APPROVAL DATE: Sep 1985

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To assess the psychosocial sequelae in patients surviving advanced Hodgkin's Disease. The hypothesis is that after controlling for treatment toxicity, longer survival time will be associated with lower psychological distress and less psychosocial disruption.

TECHNICAL APPROACH

All eligible patients are asked to consent to an interview over the telephone lasting approximately 45 minutes. questions relating to psychiatric symptoms, mood, sexual function, social adjustment, and thoughts about illness are addressed.

PRIOR AND CURRENT PROGRESS

Study closed October 1988 to patient accrual. To date a total of 39 patients have been entered.

CONCLUSIONS

To date, final analysis has not been completed.

REPORT DATE: 08/25/89

WORK UNIT # 1540-85

DETAIL SUMMARY SHEET

TITLE: CALGB 8562: Retrospective Assessment of Psychosocial and Psychosexual Sequelae in Three Treatment Regimens for Advanced Hodgkin's Disease

KEYWORDS: psychosocial, psychosexual, Hodgkin's disease

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Completed  
APPROVAL DATE: Sep 1985

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To assess the psychosocial sequelae for patients treated on CALGB 8251 with Stage III or IV Hodgkins disease one year off treatment.

TECHNICAL APPROACH

All eligible patients are asked to give consent for an interview by telephone addressing questions concerning psychosocial symptoms, mood, sexual function, psychosocial adjustment, and psychosexual adjustment.

PRIOR AND CURRENT PROGRESS

Study closed October 1988. Prior to closure, a total of eight patients were entered.

CONCLUSIONS

No significant differences were found in psychosocial and psychosexual adaptation between the three different treatment arms.

REPORT DATE: 11/02/88

WORK UNIT # 1543-86

DETAIL SUMMARY SHEET

TITLE: CALGB 8513: A Phase III Trial of Intensive Treatment for Adult Acute Lymphocytic Leukemia: A Comparison of Combination Chemotherapy plus Alternating Mitoxantrone and Daunorubicin Vs. Combination Chemotherapy plus Daunorubicin

KEYWORDS: daunorubicin, mitoxantrone, leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Completed  
APPROVAL DATE: Dec 1985

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To compare the efficacy of treating patients with acute lymphocytic leukemia with daunorubicin alone or with daunorubicin alternating with mitoxantrone. All patients receive vincristine, prednisone, methotrexate, ara-c, and 6MP.

TECHNICAL APPROACH

Randomized study in which all eligible patients are registered and randomly assigned to receive either Mitoxantrone alternating with Daunorubicin or Daunorubicin alone.

PRIOR AND CURRENT PROGRESS

Study closed March 1988. Prior to closure one additional patient was entered for a total of 11 patients to date. Relapse rate has been high. Ten of eleven patients experienced a complete remission but eight of those ten patients have since relapsed. Of the eight relapsed patients, four have expired with disease, two have undergone successful bone marrow transplants and two are currently being treated.

CONCLUSIONS

Group-wide data have been partially studied. Relapse rate is high throughout the group. Conclusion made that maintenance therapy is needed for longer period of time than the therapy provided for intensification only.

REPORT DATE: 06/27/89

WORK UNIT # 1544-86

DETAIL SUMMARY SHEET

TITLE: CALGB 8661: The Epidemiology of the Acute Leukemias in Adults with Special Reference to Cytogenetically Determined Subgroups

KEYWORDS: leukemia, Ara-C, post intensification

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Completed  
APPROVAL DATE: Dec 1985

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To evaluate the effect of intensive post-remission Ara-C on the duration of CR in patients with ANLL when given as part of an eight course consolidation regimen and compared to a lower dose Ara-C program.

TECHNICAL APPROACH

Randomized study in which all eligible patients receive Ara-C 200 mg/m<sup>2</sup> IV dx7 and Daunorubicin 45 mg/m<sup>2</sup> dx3 for remission induction therapy. If successfully in remission, the patients are then randomized to one of three regimens of Ara-C ie., 3 Grams/m<sup>2</sup>, 200 mg/m<sup>2</sup>, or 100 mg/m<sup>2</sup> for 4 months of consolidation.

PRIOR AND CURRENT PROGRESS

Study have been open since January, 1986. A total of 39 patients have been entered to date at Walter Reed Army Medical Center.

CONCLUSIONS

Data is currently being analyzed for the CALGB group.

REPORT DATE: 07/03/89

WORK UNIT # 1550-86

DETAIL SUMMARY SHEET

TITLE: CALGB 8534: Combination Chemotherapy with Intensive ACE/PCE and Radiation Therapy to the Primary Tumor and Prophylactic Whole Brain Radiation Therapy with or without Warfarin in Limited Small Cell Carcinoma of the Lung

KEYWORDS: lung, carcinoma chemotherapy, radiation

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine

SERVICE: Cancer & Leukemia Group B

STATUS: Ongoing

APPROVAL DATE: Aug 1986

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine the complete response rate and long term survival of patients treated with a new combined modality program containing three cycles of ACE followed by concurrent radiation and PCE followed by three cycles of ACE.

TECHNICAL APPROACH

Randomized study in which all eligible patients receive the above listed therapy with or without daily doses of warfarin.

PRIOR AND CURRENT PROGRESS

Two additional patients have been entered this year. To date a total of five patients are on study. All five patients are alive and are being followed. Four of five patients responded completely. One of five patients had little or no response.

CONCLUSIONS

Because of an almost 25% rate of life threatening complications occurring in last 3 cycles, group decision was made to eliminate the last 3 cycles of chemotherapy. All patients received only 5 cycles of CT, 3 before x RT and 2 during RT.

REPORT DATE: 08/27/89

WORK UNIT # 1551-86

DETAIL SUMMARY SHEET

TITLE: CALGB 8362: Pharmacokinetics of Ara-C in Patients with Acute Myelogenous Leukemia, A Companion to CALGB 8525

KEYWORDS: pharmacokinetics, ARA-C, leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Cancer & Leukemia Group B

APPROVAL DATE: Sep 1986

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To monitor the plasma levels associated with Ara-C induction therapy and the 3 dosage levels of Ara-C used in the post-remission therapy in CALGB 8525.

TECHNICAL APPROACH

Non-randomized companion study in which all eligible patients give consent to have four samples of blood drawn during induction therapy and again during the first course of intensification therapy. Blood is then processed and sent to a reference laboratory for drug levels.

PRIOR AND CURRENT PROGRESS

Study still open to accrual. To date a total of 23 patients have been entered.

CONCLUSIONS

Data are being received and summarized to determine drug concentration levels and drug clearance rates.

REPORT DATE: 10/12/88

WORK UNIT # 1552-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8694: A Randomized Comparison of m-BACOD and CHOP Chemotherapy in Advanced Stage Large Cell Lymphoma

KEYWORDS: chemotherapy, lymphoma

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Completed  
APPROVAL DATE: Nov 1986

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To compare a 4 drug standard chemotherapy regimen (CHOP) versus a 6 drug experimental regimen (m-BACOD) as therapy for diffuse large cell and diffuse mixed malignant lymphomas.

TECHNICAL APPROACH

Randomized study in which all eligible patients receive either CHOp therapy or m-BACOD therapy for 2 cycles reevaluated and receive the assigned therapy for 6 more cycles if remission has occurred.

PRIOR AND CURRENT PROGRESS

Study opened November 1986. Closed January 1988. Only two patients were entered.

CONCLUSIONS

None yet. Group analysis of the treatment aims is underway.

REPORT DATE: 09/02/89

WORK UNIT # 1554-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8691: Cytoxan with or without Interferon for Low Grade Lymphoma

KEYWORDS: cytoxan, alpha interferon, lymphoma

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine

SERVICE: Cancer & Leukemia Group B

STATUS: Ongoing

APPROVAL DATE: Dec 1986

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To compare the effectiveness of cytoxan versus cytoxan plus alpha interferon in the management of patients with nodular poorly differentiated lymphocytic and nodular mixed lymphocytic histiocytic lymphoma.

TECHNICAL APPROACH

Randomized study in which all eligible patients receive either cytoxan alone or cytoxan with alpha interferon for at least 3 months.

PRIOR AND CURRENT PROGRESS

Study has been open to accrual since January 1986. To-date only one patient has been entered. This patient was enrolled in July 1988 and is responding well to therapy.

CONCLUSIONS

None at this time.

REPORT DATE: 12/27/88

WORK UNIT # 1556-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8693: Evaluation of Adjuvant Therapy in Node Negative Operable Breast Cancer

KEYWORDS: adjuvant therapy, node negative, breast cancer

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine

STATUS: Completed

SERVICE: Cancer & Leukemia Group B

APPROVAL DATE: Jan 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To assess the impact of short term intensive chemotherapy with CMFP to prevent disease recurrence and prolong survival in node negative patients with any size of ER negative tumors and node negative patients with ER positive tumors whose pathological size is greater than 3 cm.

TECHNICAL APPROACH

Randomized study in which all eligible patients are stratified and then randomly assigned to receive chemotherapy for 6 cycles or to be just observed only.

PRIOR AND CURRENT PROGRESS

Study opened 1-87 and closed 4-88. During that long interim period only one patient was entered.

CONCLUSIONS

None. Data too sparse.

REPORT DATE: 02/22/89

WORK UNIT # 1557-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8791: A Randomized Comparison of Pentostatin Vs. Alpha Interferon in Previously Untreated Patients with Hairy Cell Leukemia

KEYWORDS: deoxycyformycin, alpha interferon, leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine

SERVICE: Cancer & Leukemia Group B

STATUS: Ongoing

APPROVAL DATE: Mar 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To compare Deoxycyformycin and Alpha-interferon with respect to frequency of response, time to response, and duration of relapse free survival among unsplenectomized patients with hairy cell leukemia.

TECHNICAL APPROACH

All eligible patients are registered and stratified to receive either alpha-interferon 3x106IU S.C. 3 times a week for 6 months or to receive deoxycyformycin 4mg/m<sup>2</sup> IV every 14 days for 6 months.

PRIOR AND CURRENT PROGRESS

Study has been open since March 1987. To date no patients have been entered.

CONCLUSIONS

Group-wide, approximately 200 patients have been entered. Data are currently being updated.

REPORT DATE: 05/16/89

WORK UNIT # 1560-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8642: A Master Protocol to Study Single Agent Chemotherapy Vs. Standard Chemotherapy for Advanced Breast Cancer

KEYWORDS: chemotherapy, cancer, breast

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Ongoing  
APPROVAL DATE: Jun 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To evaluate single Phase II agents in achieving responses in previously untreated metastatic breast cancer patients.

TECHNICAL APPROACH

Randomized study in which all eligible patients receive either standard CAF therapy or a Phase II agent. Those randomized to receive a Phase II agent are treated for two cycles then reevaluated for response or progression. If progression occurs, they are switched to CAF therapy.

PRIOR AND CURRENT PROGRESS

Study has been opened since 6-87. To date only 3 patients have been entered. Two of the three patients have expired with progressive disease. One of the three patients is alive with stable disease.

CONCLUSIONS

Data too sparse.

REPORT DATE: 05/17/89

WORK UNIT # 1562-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8742: A Phase II Study of Trimetrexate for Advanced Breast Cancer

KEYWORDS: trimetrexate, breast, cancer

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Completed  
APPROVAL DATE: Jun 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To evaluate single and/or multiple agents for significant anti-tumor activity in the treatment of inoperable, recurrent, or metastatic carcinoma of the breast. Activity will be determined by the frequency of complete or partial remission. remission.

TECHNICAL APPROACH

Non-randomized study in which all eligible patients receive Trimetrexate every day for 5 days. This course of therapy is repeated every 21 days.

PRIOR AND CURRENT PROGRESS

This study was closed to patient entry in July 1988. Prior to closure a total of only two patients were entered. Both patients progressed while on the study and have expired.

CONCLUSIONS

None.

REPORT DATE: 05/17/89

WORK UNIT # 1563-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8662: Monitoring Circulating Breast Cancer-Associated Antigens with the 15-3 Radioimmunoassay

KEYWORDS: breast cancer, antigens, radioimmunoassay

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Completed  
APPROVAL DATE: Jun 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine the clinical value of monitoring the circulating breast carcinoma associated antigen with the use of the plasma assay, CA15-3, in a prospectively followed population of patients with metastatic breast cancer.

TECHNICAL APPROACH

Non-randomized companion study to any of the ongoing metastatic breast cancer treatment protocols in which all eligible patients are registered only. On the day of initial therapy and every month thereafter as well as at the time of disease progression, a ten cc sample of blood is drawn, centrifuged, frozen, then sent to an approved CALGB reference laboratory for radioimmunoassay.

PRIOR AND CURRENT PROGRESS

Study was closed October 21, 1988. Prior to closure, ten patients were entered from WRAMC.

CONCLUSIONS

Data from group being analyzed. Preliminary report will be available in fall 1989.

REPORT DATE: 05/17/89

WORK UNIT # 1564-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8692: Intergroup Study in Metastatic Sarcomas

KEYWORDS: chemotherapy, sarcoma

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Cancer & Leukemia Group B

APPROVAL DATE: Jun 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine if the addition of ifosfamide to doxorubicin and dacarbazine significantly changes the response rate, survival, and toxicity in the therapy of metastatic soft tissue sarcomas.

TECHNICAL APPROACH

Randomized study in which all eligible patients receive either Doxorubicin and Dacarbazine alone or Doxorubicin, Dacarbazine, and Ifosfamide with Mesna.

PRIOR AND CURRENT PROGRESS

Study is still open to patient entry. To date a total of nine patients have been entered. One of nine had a complete response to therapy. Eight of nine patients had progressive disease or stable disease with therapy.

CONCLUSIONS

Groupwide data currently being collected and interpreted.

REPORT DATE: 08/09/89

WORK UNIT # 1565-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8695: Combination Chemotherapy for Advanced Hodgkin's Disease

KEYWORDS: chemotherapy, Hodgkin's disease

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine

STATUS: Completed

SERVICE: Cancer & Leukemia Group B

APPROVAL DATE: Jun 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To compare the effectiveness of the MOPP/ABV Hybrid with sequential MOPP cross over to ABVD in patients with advanced or recurrent Hodgkins disease and to determine which regimen is superior with respect to the following parameters: complete response rate , duration of CR, freedom from progression, and survival.

TECHNICAL APPROACH

Randomized study in which all eligible patients receive either MOPP for 6 cycles followed by ABVD for 3 cycles or the MOPP/ABV Hybrid for 6 cycles.

PRIOR AND CURRENT PROGRESS

Study opened June 1989 and closed July 1989. During that period of time a total of eight patients were entered at WRAMC. All eight patients have been CR's or PR's and are alive. Accrual has been met groupwide and results of the study are being compiled.

CONCLUSIONS

Results currently being tabulated and data being studied by PI.

REPORT DATE: 06/12/89

WORK UNIT # 1567-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8711: Idarubicin in Acute Lymphocytic Leukemia, Relapsed or Failed Induction

KEYWORDS: idarubicin, lymphocytic leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Ongoing  
APPROVAL DATE: Jul 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To test the remission induction rate of the Idarubicin regimen. To identify the toxicity of the Idarubicin regimen. To investigate the feasibility of a consolidation regimen containing Idarubicin and Ara-C.

TECHNICAL APPROACH

Study has no randomization. All eligible patients receive Idarubicin 12.5 mg/m<sup>2</sup> on days 1, 2, and 3. If remission is documented, Idarubicin and Ara-C are given as consolidation therapy. If remission does not occur, reinduction with Idarubicin.

PRIOR AND CURRENT PROGRESS

Study has been open since July 1987. To date a total of four patients were entered. Three of the four died without responding to the therapy. One of the four is alive and has had a successful bone marrow transplant.

CONCLUSIONS

None. Data too sparse.

REPORT DATE: 06/12/89

WORK UNIT # 1568-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8741: A Dose Response Trial of Megace for Advanced Breast Cancer

KEYWORDS: megace, breast, cancer

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Cancer & Leukemia Group B

APPROVAL DATE: Jul 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To evaluate dose-response relationship for megestrol acetate. To determine relative dose and toxicity to optimize dosing for megestrol acetate. To compare the 3 dose levels according to the following endpoints: response frequency, time to progression, time to chemotherapy, and time to visceral disease and survival.

TECHNICAL APPROACH

Randomized study in which all eligible patients receive one of 3 dose levels of Megace: 160mg, 800 mg, or 1600 mg per day.

PRIOR AND CURRENT PROGRESS

Study has been open since 7-87. Two patients were entered in 1987, five in 1988, and one patient in 1989 for a total of seven patients. Two patients have expired with progressive disease. One patient was removed from study because of disease progression. The remaining four patients have remained on study with either stable or partial responses.

CONCLUSIONS

None at this time.

REPORT DATE: 10/12/88

WORK UNIT # 1571-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8721: A Phase II Trial of Sequential High Dose ARA-C and L-Asparaginase for Acute Non-Lymphocytic Leukemia

KEYWORDS: ara-c, l-asparaginase, myelocytic leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Cancer & Leukemia Group B

APPROVAL DATE: Oct 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To assess the efficacy of HiDAC/L-asp for remission induction and duration in patients with ANLL following an antecedent hematologic disorder an/or cytotoxic chemotherapy and/or radiation.

TECHNICAL APPROACH

Non-randomized study in which all eligible patients are registered to receive ara-c 3 gm/m<sup>2</sup> of 12 hours time 2 followed by L-Asparaginase 6,000 IU/m<sup>2</sup> IM or SC at hour 39.

PRIOR AND CURRENT PROGRESS

None. Study opened October 1987. Just one patient has been entered and that patient started therapy yesterday October 11, 1988.

CONCLUSIONS

None.

REPORT DATE: 10/12/88

WORK UNIT # 1572-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8736: Combined Chemotherapy and Radiotherapy for Stage III Lung Cancer

KEYWORDS: chemotherapy, radiotherapy, lung cancer

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Completed  
APPROVAL DATE: Oct 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine in a randomized controlled trial whether those patients initially treated with chemotherapy (VBL/DDP) and radiation therapy will have more prolonged remission and/or survival if given post RT chemotherapy (VBL/CBDCA) than a comparable group assigned only to observation following radiation therapy.

TECHNICAL APPROACH

Non-randomized study in which all eligible patients are registered and receive chemotherapy followed by radiotherapy. Patients are then randomized to receive either post radiation chemotherapy or no further treatment.

PRIOR AND CURRENT PROGRESS

None. Study opened October 1987 and closed February 1988. No patients were entered.

CONCLUSIONS

This is a final report.

REPORT DATE: 10/12/88

WORK UNIT # 1573-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8762: Molecular Subtypes in Acute Lymphatic Leukemia with Philadelphia Chromosome

KEYWORDS: ALL, Philadelphia chromosome

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Ongoing  
APPROVAL DATE: Oct 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine the incidence of pH positivity as detected by molecular methods in consecutive patients with previously untreated Acute Lymphatic Leukemia.

TECHNICAL APPROACH

Non-randomized study in which all eligible patients are registered. At entry, at first intensification, at remission or 6 months and at relapse samples of marrow and blood are sent to the CALGB reference laboratory for analysis.

PRIOR AND CURRENT PROGRESS

Study has been open since October 1987. To date only one patient has been entered.

CONCLUSIONS

None.

REPORT DATE: 10/12/88

WORK UNIT # 1574-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8763: Immunoglobulin and T Cell Receptor Gene Rearrangement in Adult Acute Lymphatic Leukemia

KEYWORDS: immunoglobulin, T-cell receptor, ALL

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Ongoing  
APPROVAL DATE: Oct 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine the incidence of Ig and T-cell receptor gene rearrangements from samples of consecutive patients with previously untreated adult ALL.

TECHNICAL APPROACH

Non-randomized study in which all eligible patients are registered only at entry prior to first intensification, at CR , at 6 months and at relapse 2 cc of marrow and 10 cc of blood are sent to CALGB reference laboratory for analysis.

PRIOR AND CURRENT PROGRESS

None. Study has been open since october 1987. To date no patients have been entered.

CONCLUSIONS

None.

REPORT DATE: 10/12/88

WORK UNIT # 1575-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8765: Analysis of Proto-Oncogene Expression in Acute Myelogenous Leukemia

KEYWORDS: proto-oncogene, leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine

SERVICE: Cancer & Leukemia Group B

STATUS: Ongoing

APPROVAL DATE: Oct 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine the incidence and clinical significance of proto-oncogene expression in ANLL Blasts.

TECHNICAL APPROACH

Prior to initiation of therapy and at relapse 2 ccs of marrow and 10 ccs of blood are sent to a CALGB reference laboratory for analysis.

PRIOR AND CURRENT PROGRESS

Study has been open since October 1987. To date a total of 11 patients have been entered.

CONCLUSIONS

None yet.

REPORT DATE: 10/12/88

WORK UNIT # 1576-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8766: Immunologic and Molecular Diagnostic Studies in Chronic Lymphatic Leukemia

KEYWORDS: immunology, lymphocytic leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Ongoing  
APPROVAL DATE: Oct 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine the incidence of the expression of the antigens in peripheral blood samples of consecutive patients with previously untreated CLL.

TECHNICAL APPROACH

Non-randomized study in which all eligible patients are registered only. At study entry 10-20 ml of blood is collected and mailed by courier to a CALGB reference laboratory for analysis.

PRIOR AND CURRENT PROGRESS

Study opened December 1987 to date a total of 12 patients have been registered and appropriate samples obtained.

CONCLUSIONS

None.

REPORT DATE: 12/27/88

WORK UNIT # 1577-80

DETAIL SUMMARY SHEET

TITLE: CALGB 8361: Immunologic Diagnostic Studies in AML (blood drawing phase); previously CALGB 7921) CALGB 8321: A Comparative Study of 3 Remission Induction Regimens and 2 Maintenance Regimens for AML (treatment phase); previously CALGB 7921

KEYWORDS: immunology, oncology, leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Ongoing  
APPROVAL DATE: Jan 1980

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0 .

STUDY OBJECTIVE

a) To determine the incidence of various markers in Acute Myelogenous Leukemia (AML); b) to correlate the presence of these markers and the surface antigen phenotype they determine with the FAB histological classification; c) to correlate the presence of the various markers with the initial and subsequent clinical characteristics of the disease.

TECHNICAL APPROACH

All eligible patients are registered prior to the initial therapy. From the diagnostic bone marrow procedure, 2 cc of bone marrow and 7 cc of peripheral blood are collected and sent by express mail to the CALGB reference laboratory for analysis and confirmation of classification. Samples are again obtained at relapse.

PRIOR AND CURRENT PROGRESS

Study is still open and accrual continues. To date a total of 48 patients have been entered at WRAMC.

CONCLUSIONS

Surface marker analysis in AML can be used to develop a unique classification system in AML that will provide information not obtainable by morphology or cytochemistry.

REPORT DATE: 01/03/89

WORK UNIT # 1577-88

DETAIL SUMMARY SHEET

TITLE: CALGB 8722 Comparison of Three Drug Combinations in Acute Non-Lymphocytic Leukemia: Relapsed or Failed Induction

KEYWORDS: acute, non-lymphocytic, leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Ongoing  
APPROVAL DATE: Jan 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To screen combination chemotherapy programs for significant activity in refractory or relapsed adult ANLL activity will be determined by CR or PR response frequency, duration and survival.

TECHNICAL APPROACH

Randomized study in which all eligible patients review a combination of DHAD and AZQ and VP-16.

PRIOR AND CURRENT PROGRESS

Study opened 1-88 to date only four patients have been entered. Two of four patients have expired with their disease. One of four patients is alive with disease and one of four patients is currently being treated.

CONCLUSIONS

None.

REPORT DATE: 01/03/89

WORK UNIT # 1578-88

DETAIL SUMMARY SHEET

TITLE: CALGB 8733: Pace and Gamma Interferon for Extensive Stage Small Cell Lung Cancer, Phase II

KEYWORDS: chemotherapy, interferon, small cell lung CA

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Completed  
APPROVAL DATE: Jan 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To assess activity of combination therapy programs using biological response modifiers in extensive SCLC activity will be determined by frequency, magnitude, and duration of response.

TECHNICAL APPROACH

Non-randomized study in which all eligible patients receive PACE as induction therapy for 4 cycles. At this point patients are re-evaluated for CR or PR and then started on Gamma Interferon therapy up to one year or until progression.

PRIOR AND CURRENT PROGRESS

None. Study opened January 1988 and closed August 1988. No patients were entered.

CONCLUSIONS

None.

REPORT DATE: 12/27/88

WORK UNIT # 1579-88

DETAIL SUMMARY SHEET

TITLE: CALGB 8861: Monitoring Circulating Breast Cancer-Associated 15-3 Antigen in Stage II Breast Cancer

KEYWORDS: antigen, breast carcinoma

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Ongoing  
APPROVAL DATE: Jan 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To evaluate the predictive value of rising CA15-3 levels in patients who are clinically free of recurring disease.

TECHNICAL APPROACH

Ten ccs of whole blood are collected prior to first therapy, at 28 days during therapy, at 4 mo for 2 years and every 6 months for four years. Blood is processed here and shipped to CALGB approved reference laboratory for analysis.

PRIOR AND CURRENT PROGRESS

None. Study opened to group accrual only 12/26/88. No patients have been entered yet.

CONCLUSIONS

None.

REPORT DATE: 02/22/89

WORK UNIT # 1580-88

DETAIL SUMMARY SHEET

TITLE: CALGB 8712: Two Types of Interferon for Previously Untreated Chronic Myelogenous Leukemia: A Phase II Study

KEYWORDS: interferon, chronic myelogenous, leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Ongoing  
APPROVAL DATE: Mar 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine whether the sequential combination of IFN-gamma and IFN alpha can reduce the percent of phi1 chromosome positive cells in previously untreated chronic phase CML.

TECHNICAL APPROACH

Non-randomized study in which all eligible patients are registered; then receive gamma IFN each day x 7 alternating with alpha INF each day x 7.

PRIOR AND CURRENT PROGRESS

Study has been open one year and to date a total of four patients have been entered.

CONCLUSIONS

No meaningful response data available yet. Toxicities may be greater during administration of gamma interferon.

REPORT DATE: 02/22/89

WORK UNIT # 1581-80

DETAIL SUMMARY SHEET

TITLE: CALGB 8363: Clonal Excess Determination in Non-Hodgkin's Lymphoma  
(Blood drawing phase); previously CALGB 7851/7951 (Treatment phase)

KEYWORDS: clonal excess, lymphoma, non-Hodgkin's

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Ongoing  
APPROVAL DATE: Apr 1980

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To monitor clonal excess in peripheral blood of patients with B cell lymphomas on defined protocols in a prospective, sequential fashion.

TECHNICAL APPROACH

Non-randomized companion protocol to existing CALGB lymphoma treatment protocols. Eligible patients submit 50cc of peripheral blood prior to being initially treated, again at the time of their CR, and then every 4 months until relapse or at relapse.

PRIOR AND CURRENT PROGRESS

No further patients have been entered this year. To date a total of 16 patients have been enrolled at WRAMC. The study is still open to accrual.

CONCLUSIONS

Major analysis of group's data is underway and results will be available soon.

REPORT DATE: 06/12/89

WORK UNIT # 1581-88

DETAIL SUMMARY SHEET

TITLE: CALGB 8831: Combined Chemotherapy and Radiotherapy for Stage III Lung Cancer

KEYWORDS: chemotherapy, radiotherapy, non small cell lung

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Cancer & Leukemia Group B

APPROVAL DATE: Jul 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine the relative toxicities of two regimens for locally advanced NSCLC.

TECHNICAL APPROACH

Randomized study in which all eligible patients receive chemotherapy ie. cisplatin and velgan followed by RT followed by chemotherapy again or receive chemotherapy ie. cisplatin and velgan followed by RT and chemotherapy simultaneously.

PRIOR AND CURRENT PROGRESS

Study opened in July 1988. To date a total of eight patients have been entered. Seven of the eight have responded to therapy to date. One of the eight was registered and treated last week.

CONCLUSIONS

None.

REPORT DATE: 06/12/89

WORK UNIT # 1582-88

DETAIL SUMMARY SHEET

TITLE: CALGB 8851: A Phase II Study of Amonafide in Refractory Lymphoma

KEYWORDS: amonafide, lymphoma

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Cancer & Leukemia Group B

APPROVAL DATE: Jul 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To evaluate the activity of amonafide chemotherapy for refractory NHL. To evaluate the toxicity of amonafide chemotherapy.

TECHNICAL APPROACH

Non-randomized study in which all eligible patients receive amonafide 300 mg/m<sup>2</sup> d x 5 every 21 days.

PRIOR AND CURRENT PROGRESS

None. The study was opened July 1988. To date no patients have been entered.

CONCLUSIONS

None.

REPORT DATE: 06/12/89

WORK UNIT # 1583-88

DETAIL SUMMARY SHEET

TITLE: CALGB 8862: A Pharmacodynamic Study of Amonafide

KEYWORDS: amonafide, pharmacodynamics

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Ongoing  
APPROVAL DATE: Jul 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine feasibility of conducting a multi-institutional pharmacodynamic study employing limited sampling points. To examine the relationships between pharmacokinetic characteristics of amonafide and clinical outcome.

TECHNICAL APPROACH

All eligible patients give consent for the collection of blood samples (30cc each prior to treatment, 45 minutes and 24 hours after treatment for 1 course of therapy only. Blood is then processed and sent to a CALGB reference laboratory for analysis.

PRIOR AND CURRENT PROGRESS

None. Study opened July 1988. To date no patients have been entered.

CONCLUSIONS

None.

REPORT DATE: 08/27/89

WORK UNIT # 1584-88

DETAIL SUMMARY SHEET

TITLE: CALGB 8896: An Intergroup Study of Adjuvant Therapy of Primary Colon Cancer

KEYWORDS: chemotherapy, adjuvant, colon Ca

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Ongoing  
APPROVAL DATE: Sep 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To compare relative toxicity and efficacy of three approaches (low dose leukovarin + 5FU, high dose leukovarin + 5-FU, observation) to treatment of patients with Dukes B or C colon cancer post-curative surgery.

TECHNICAL APPROACH

Randomized study in which all eligible patients are stratified according to extent, obstruction and metastasis to received surgery alone or surgery followed by low dose chemotherapy or high dose chemotherapy.

PRIOR AND CURRENT PROGRESS

Study has been open here at WRAMC since September 1988. To date, no patients have been entered.

CONCLUSIONS

None.

REPORT DATE: 08/28/89

WORK UNIT # 1585-88

DETAIL SUMMARY SHEET

TITLE: CALGB 8834: A Randomized Phase II Study of Chemotherapy for Advanced Non-small Cell Lung Cancer

KEYWORDS: chemotherapy, lung cancer

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine  
SERVICE: Cancer & Leukemia Group B

STATUS: Completed  
APPROVAL DATE: Sep 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To screen single or combination chemotherapy programs and/or Biological Response Modifiers for significant activity in metastatic NSLC or in locally advanced NSLLC because of malignant pleural effusion.

TECHNICAL APPROACH

Randomized study in which all eligible patients receive either 6-thioguanine IV qd x 5 or Cis-Platin + FU.

PRIOR AND CURRENT PROGRESS

Study was opened September 1988 and closed April 1989. During that period of time only two patients were entered. One has expired and one is alive with disease.

CONCLUSIONS

Group-wide, a total of 65 patients were entered. Data collection is not yet completed.

REPORT DATE: 04/01/88

WORK UNIT # 1236

DETAIL SUMMARY SHEET

TITLE: Plasma Beta-endorphin, Cortisol, Catecholamines and Cyclic Nucleotide Responses in Asymptomatic Individuals Undergoing Repeat Treadmill Testing

KEYWORDS: neuroendocrine, treadmill, coronary disease

PRINCIPAL INVESTIGATOR: Zoltick, Jerel MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Cardiology Service

STATUS: Ongoing  
APPROVAL DATE: May 1984

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

This study is a single-blind analysis of plasma neurohormone levels during repeat treadmill testing in subjects with abnormal treadmill tests. The control group consists of a maximal treadmill test during which time blood is collected for beta-endorphin, catecholamines, cyclic nucleotides and cortisol.

TECHNICAL APPROACH

This study is a single-blind analysis of plasma neurohormone levels during repeat treadmill testing in subjects with abnormal treadmill tests. The control group consists of adult males with no evidence of abnormal electrocardiographic findings on treadmill testing and low risk factors for cardiovascular disease. The study consists of a maximal treadmill test during which time blood is collected for beta-endorphin, catecholamines, cyclic nucleotides and cortisol.

PRIOR AND CURRENT PROGRESS

Plasma norepinephrine, epinephrine, prolactin, B-endorphin and ACTH levels increased dramatically in nearly all control subjects during maximal treadmill exercise (an index of fitness). The changes in plasma levels of B-endorphin and ACTH in control subjects of fifteen minutes after maximal exercise were negatively correlated with the duration of maximal exercise. Subjects with coronary artery disease (CAD) were able to perform treadmill exercise sufficient to increase plasma levels of B-endorphin and ACTH but not prolactin.

CONCLUSIONS

Neuroendocrine responses in control subjects are similar at the equivalent relative exercise intensity (brief vigorous exercise to exhaustion) regardless of fitness. The failure of CAD subjects to increase prolactin levels with exercise may reflect an inability to sustain anaerobic metabolism, a necessary condition for PRL release. FY89 data was not available at the time of publication.

REPORT DATE: 01/12/90

WORK UNIT # 1238

DETAIL SUMMARY SHEET

TITLE: Effect of Heart Disease on Quality of Life

KEYWORDS: heart disease, treatment, quality of life

PRINCIPAL INVESTIGATOR: Weston, Lawrence CPT MC

DEPARTMENT: Department of Medicine  
SERVICE: Cardiology Service

STATUS: Terminated

APPROVAL DATE: Mar 1985

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

Using questionnaire methodology, assess patients "Quality of Life" before and after therapy for heart disease. There has been no change in the original protocol.

TECHNICAL APPROACH

There have been no modifications to the protocol's methods.

PRIOR AND CURRENT PROGRESS

In the last year only 63 patients have been newly enrolled into the study. As was the case last year, patient enrollment was left to individual physicians, which has been sporadic. Future enrollment is expected to improve if outside funding becomes available to hire a nurse to assist in patient enrollment and data collection.

CONCLUSIONS

ADMINISTRATIVELY TERMINATED.

REPORT DATE: 01/26/89

WORK UNIT # 1243

DETAIL SUMMARY SHEET

TITLE: Percutaneous Balloon Valvuloplasty for Patients with Mitral Stenosis or Aortic Stenosis: A Pilot Study

KEYWORDS: valvuloplasty, aortic stenosis, mitral stenosis

PRINCIPAL INVESTIGATOR: Moore, John LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Cardiology Service

STATUS: Ongoing  
APPROVAL DATE: Oct 1986

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine the efficacy of percutaneous balloon valvuloplasty in adults with aortic or mitral stenosis.

TECHNICAL APPROACH

Symptomatic patients with mitral stenosis and aortic stenosis will be offered PBV as an option to standard surgical valve replacement. RBV will be performed with immediate and short term (6 mos) hemodynamic, angiographic and echocardiographic evaluation.

PRIOR AND CURRENT PROGRESS

A total of 40 patients (23 aortic, 17 mitral) have been enrolled; 17 in 1988 (10 aortic, 7 mitral) in 1988, 2 procedural deaths in patients with aortic stenosis occurred. Follow-up to date indicated marked symptomatic, functional and hemodynamic improvements in mitral patients. Aortic patients have been plagued by the problem of restenosis and poor survival due to advanced age and multiple compounding medical problems.

CONCLUSIONS

Mitral valvuloplasty and aortic valvuloplasty appear to be effective alternatives to valve replacement in selected individuals; however long-term follow-up is required.

REPORT DATE: 05/16/89

WORK UNIT # 1245

DETAIL SUMMARY SHEET

TITLE: A Double Blind Study of the Safety and Efficacy of Multiple Intravenous Infusions of Disodium EDTA in Patients with Obstructive Peripheral Arterial Disease and Intermittent Claudication

KEYWORDS: EDTA, claudication

PRINCIPAL INVESTIGATOR: Ross, Terence MAJ MC

ASSOCIATES: Bigham, Peter CPT MC

DEPARTMENT: Department of Medicine  
SERVICE: Cardiology Service

STATUS: Ongoing  
APPROVAL DATE: Jul 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To evaluate the intravenous administration of EDTA in subjects with peripheral vascular disease manifested by intermittent claudication.

TECHNICAL APPROACH

Thirty weekly intravenous administrations at 2 different dosage levels will be given. The effect on the symptom of exercise tolerance will be compared and the drug response will be evaluated by measuring the distances walked during treadmill examination.

PRIOR AND CURRENT PROGRESS

At the present time seven patients have met initial screening criteria and are eligible to be initiated into the protocol. Funding through the Jackson Foundation has finally been received as of 24 April 1989. A nurse is presently being placed on the payroll to allow administration of EDTA infusions and data collection. Active recruitment of patients is ongoing.

CONCLUSIONS

No conclusions from the study are available at present, given the lack of completion of the treatment phase for any patient.

REPORT DATE: 10/04/89

WORK UNIT # 1246

DETAIL SUMMARY SHEET

TITLE: Diltiazem in the Treatment of Raynaud's Phenomenon: An Objective Double-Blind Study

KEYWORDS: diltiazem, Raynaud's disease

PRINCIPAL INVESTIGATOR: Cambier, Patrick CPT MC

DEPARTMENT: Department of Medicine  
SERVICE: Cardiology Service

STATUS: Completed  
APPROVAL DATE: Oct 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

Treat condition known as Raynaud's disease, a painful vasospastic condition of extremities, using the calcium antagonist, diltiazem.

TECHNICAL APPROACH

Double blind, placebo controlled trial utilizing diltiazem and placebo drug trials. Skin temperature after submersion into ice water is measured, along with sensation of improvement.

PRIOR AND CURRENT PROGRESS

Fourteen patients enrolled, majority experienced benefit. Data collected and evaluated. No adverse effects of clinical significance. Paper presented at US Army Regional American College of Physicians Meeting, 1988 and the National American College of Physicians Meeting, 1989.

CONCLUSIONS

Diltiazem is a safe and effective agent to reduce the severity and frequency of painful Raynaud's vasospasm.

REPORT DATE: 10/26/89

WORK UNIT # 1247

DETAIL SUMMARY SHEET

TITLE: An Open Multicenter Single-Dose Safety and Efficacy Study of BW tPA in Patients with Acute Myocardial Infarction

KEYWORDS:

PRINCIPAL INVESTIGATOR: Martyak, Thomas MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Cardiology Service

STATUS: Terminated  
APPROVAL DATE: Oct 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

ADMINISTRATIVELY TERMINATED DUE TO LACK OF REPORT.

TECHNICAL APPROACH

ADMINISTRATIVELY TERMINATED DUE TO LACK OF REPORT

PRIOR AND CURRENT PROGRESS

ADMINISTRATIVELY TERMINATED DUE TO LACK OF REPORT.

CONCLUSIONS

ADMINISTRATIVELY TERMINATED DUE TO LACK OF REPORT.

REPORT DATE: 10/04/88

WORK UNIT # 1248

DETAIL SUMMARY SHEET

TITLE: A Study of the Efficacy and Safety of the Modified Mansfield Heart Trak III Low Profile PTCA Catheter

KEYWORDS: PTCA, catheter

PRINCIPAL INVESTIGATOR: Ross, Terence MAJ MC

ASSOCIATES: White, Christopher MAJ MC; Ramee, Stephen MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Cardiology Service

STATUS: Completed  
APPROVAL DATE: Dec 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To evaluate the safety and efficacy of the modified heart trak III, low profile PTCA catheter in dilatine coronary stenoses.

TECHNICAL APPROACH

The new PTCA catheter was used in a standard manual dirine elective PTCA.

PRIOR AND CURRENT PROGRESS

Five patients were enrolled prior to study termination. No serious or adverse effects occurred and no patients were withdrawn. The catheter was successful and benefited all patients by relieving coronary steloses.

CONCLUSIONS

The PTCA catheter appears to be safe and effective in dilitine coronary stenoses.

REPORT DATE: 10/16/89

WORK UNIT # 1249

DETAIL SUMMARY SHEET

TITLE: Multicenter Study of Silent Ischemia

KEYWORDS: silent, ischemia

PRINCIPAL INVESTIGATOR: Rogan, Kevin MAJ MC

ASSOCIATES: Gorman, Patrick CPT MC

DEPARTMENT: Department of Medicine  
SERVICE: Cardiology Service

STATUS: Ongoing

APPROVAL DATE: Dec 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

Heart patients can have brief episodes of silent myocardial ischemia which is reflected on the electrocardiogram without accompanying symptoms. The meaning of ischemia without symptoms is uncertain. The purpose of this study is to find out whether silent ischemia is a predictor of future complications such as myocardial infarction, development of unstable angina or sudden death.

TECHNICAL APPROACH

One to six months after hospitalization for acute MI, unstable angina or congestive heart failure with ischemic etiology, study subjects will have a physical exam, cardiovascular history taken, a 24-hour holter recording, routine ECG, a thallium exercise test and be asked to fill out a psychological profile questionnaire. Follow-up visits include a brief interview to assess health status, and on some occasions, an ECG. The 24 hour holter is repeated once (at the first follow-up visit).

PRIOR AND CURRENT PROGRESS

As of December 1988, twelve subjects had been enrolled at Walter Reed. As of this date, 26 subjects have been enrolled. There have been no serious or unexpected adverse reactions. Five subjects have been placed on inactive status: one due to endpoint event; two because of patient refusal to continue; one due to co-morbidity and one because of recurrent cardiac events. Patients benefit in that the testing program provides an unusually frequent and detailed series of health evaluations, as well as opportunities for health education.

CONCLUSIONS

The Multicenter Study of Silent Myocardial Ischemia is only in the data collection phase. No data have been analyzed as of yet. The data collection phase is expected to last until May 1991.

REPORT DATE: 12/28/89

WORK UNIT # 1250

DETAIL SUMMARY SHEET

TITLE: The Cardiointegram for Detecting Coronary Artery Disease: A Retrospective Study

KEYWORDS: cardiointegram, coronary disease

PRINCIPAL INVESTIGATOR: Laird, John CPT MC

ASSOCIATES: Weston, Lawrence MAJ MC; White, Christopher MD

DEPARTMENT: Department of Medicine  
SERVICE: Cardiology Service

STATUS: Completed

APPROVAL DATE: Feb 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To test the sensitivity and specificity of the cardiointegram, a computer generated transformation of a standard ECG integrating voltage over time, for the detection of coronary artery disease.

TECHNICAL APPROACH

Data was obtained retrospectively using the cardiac catheterization data base and machine readable ECG's stored on the Marquette (KAPOC) computer system. ECG's were retrieved for those patients with normal resting ECG's who underwent coronary angiography from mid 1986 to mid 1988 for suspected coronary artery disease. The ECG was processed by the Cardiointegram and was graded as either normal or abnormal. The results were correlated with the angiographic findings of the presence or absence of obstructive coronary artery disease. The sensitivity and specificity of the test could then be obtained.

PRIOR AND CURRENT PROGRESS

Three thousand fifty-four patients were included in the study, of which 320 were found to have ECG's stored in the KAPOC computer system that were interpreted as either normal, borderline normal, or "otherwise normal." Of these 320 digitally stored exclusions, 122 patients were included in the final analysis. The cardiointegram were graded as normal or abnormal and the results were correlated with the angiographic findings. The Cardiointegram was found to have a sensitivity of 49% and a specificity of 56% for the detection of coronary artery disease in the population being studied.

CONCLUSIONS

The Cardiointegram was neither sensitive nor specific for the detection of coronary artery disease. It would appear that its utility as a screening test for coronary artery disease in patients with a normal ECG is limited.

REPORT DATE: 12/28/89

WORK UNIT # 1251

DETAIL SUMMARY SHEET

TITLE: Noninvasive Estimation of Prosthetic Aortic Valve Area Using Doppler Ultrasound

KEYWORDS: doppler, prosthetic, aortic valve

PRINCIPAL INVESTIGATOR: Laird, John CPT MC

ASSOCIATES: Hoadley, Steven MD; Highfill, William MD

DEPARTMENT: Department of Medicine  
SERVICE: Cardiology Service

STATUS: Completed  
APPROVAL DATE: Mar 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine if Doppler ultrasound, using the equation, can accurately estimate the effective area of prosthetic valves in the aortic position.

TECHNICAL APPROACH

Patients who have undergone aortic valve replacement within the past year (prosthetic and bioprosthetic) and those patients undergoing valve replacement in the future will be studies with Doppler echo to include the use of the continuity equation to estimate the prosthetic valve area. This will be compared with the predetermined effective orifice area to assess the effectiveness of this technique for the evalution of prosthetic valve function.

PRIOR AND CURRENT PROGRESS

Because of the advent of newer technologies, i.e. transesophageal echocardiography, the techniques being evaluated in this study have already become outdated. For this reason, the study was terminated after collecting data on a small number of patients. Transesophageal echo has revolutionized the way in which prosthetic valves can be studied non-invasively.

CONCLUSIONS

None.

REPORT DATE: 05/08/89

WORK UNIT # 1252

DETAIL SUMMARY SHEET

TITLE: Assessment of the Effect of Mental Arousal on Cardiac Function

KEYWORDS:

PRINCIPAL INVESTIGATOR: Dykstra, Gary MAJ MC  
ASSOCIATES: Krantz, David PhD; Zoltick, Jerrell MD

DEPARTMENT: Department of Medicine  
SERVICE: Cardiology Service

STATUS: Ongoing  
APPROVAL DATE: Apr 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine the effects of mental stress on the patient with myocardial ischemia.

TECHNICAL APPROACH

Evaluation of patients with known atherosclerotic heart disease by means of bicycle exercise with echocardiography, and holter monitoring for ST segment changes reflective of ischemia as well as subjecting these same patients to standard mental stress testing performed simultaneously with echocardiography to look for changes in wall motion indicative of ischemia. Patients will also undergo serum testing for catecholamine levels, etc., to assess biochemically, the effects of such stress.

PRIOR AND CURRENT PROGRESS

No patients entered.

CONCLUSIONS

None

REPORT DATE: 05/08/89

WORK UNIT # 1253

DETAIL SUMMARY SHEET

TITLE: Diastolic Dysfunction of the Left Ventricle as a Predictor of  
Doxorubicin Cardiotoxicity: A Pilot Study

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rogan, Kevin MAJ MC  
ASSOCIATES: Dykstra, Gary; Norby, Eric

DEPARTMENT: Department of Medicine  
SERVICE: Cardiology Service

STATUS: Ongoing  
APPROVAL DATE: May 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine the ability of non-invasive techniques such as Doppler and MUGA testing of diastolic function to assess early complications of Adriamycin therapy on cardiac function. Are these tests as good as endomyocardial biopsy? Are they good at early discrimination of cardiac toxicity?

TECHNICAL APPROACH

Comparison of standard Doppler parameters of diastolic function (Peak filling rates, early/late diastolic filling ratios) and MUGA parameters of diastolic function (Time to peak filling, peak filling rate) with end myocardial biopsy and invasive hemodynamic monitoring in patients who are to receive Adriamycin. Serial assessment by non-invasive means is done at time zero, after 150 mg/M2 of Adriamycin, and after 300 mg/M2. Biopsy is performed at 300 mg/M2.

PRIOR AND CURRENT PROGRESS

No patients entered.

CONCLUSIONS

None.

REPORT DATE: 08/25/89

WORK UNIT # 1254

DETAIL SUMMARY SHEET

TITLE: Cardiac Arrhythmia Suppression Trial (CAST)

KEYWORDS: arrhythmia, therapy, myocardial infarction

PRINCIPAL INVESTIGATOR: Weston, Lawrence MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Cardiology Service

STATUS: Ongoing  
APPROVAL DATE: May 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

CAST is a randomized, multicenter, placebo-controlled trial to test whether suppression of asymptomatic ventricular arrhythmias after MI would reduce the rate of death from arrhythmia.

TECHNICAL APPROACH

Patients meeting the only criteria were treated in an open label fashion with either encainide, flecainide or moricizine. Following documentation of suppression of ventricular ectopy by one of the study drugs the patients were randomized to either the active drug or placebo. Thereafter the patients were followed for any of the study end points which included cardiac death and arrhythmia death.

PRIOR AND CURRENT PROGRESS

In March, 1989, after recruitment of 2309 patients, the data and safety monitoring board recommended that encainide and flecainide be discontinued because of an excess mortality in those patients assigned to active drug. (see list of publications). All remaining patients of encainide/flecainide randomized therapy were allowed to be controlled in the moricizine arm of the protocol and patients currently entering the study are exposed to moricizine therapy only. Continuation of the CAST study is expected with or without the addition of alternate study drug.

CONCLUSIONS

Neither encainide or flecainide should be used to treat asymptomatic ventricular arrhythmias after myocardial infarction. Whether the adverse effects of these two drugs represents proarrhythmia remains to be answered by continuation of the study.

REPORT DATE: 03/20/89

WORK UNIT # 1805

DETAIL SUMMARY SHEET

TITLE: Use of Isotretinoin in Prevention of Basal Cell Carcinoma

KEYWORDS: basal cell, prevention, isotretinoin

PRINCIPAL INVESTIGATOR: Benson, Paul MAJ MC

ASSOCIATES: Sperling, Leonard MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Dermatology Service

STATUS: Ongoing

APPROVAL DATE: May 1983

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

a) To evaluate the effectiveness of low dosage levels of isotretinoin in reducing the incidence of basal cell carcinomas in a high risk population; b) to examine possible side effects associated with long term administration of low doses of isotretinoin.

TECHNICAL APPROACH

The study is a double-blind randomized clinical trial to evaluate the efficacy of isotretinoin in reducing the incidence of basal cell carcinoma.

A minor modification to the original protocol made during the previous year is two consecutive fasting triglyceride values less than 211 mg % are required within three months prior to randomization.

Modification to the original protocol made during the year 1987 recommended a change in interim x-rays. Interim x-rays will only be taken on subjects noted to have DISH documented on the baseline visit (study entry) roentgenogram.

PRIOR AND CURRENT PROGRESS

The recruitment phase of the study closed 26 June 1987 with 135 randomized study participants consisting of 110 males and 25 females. Currently, 74 subjects have completed the three year intervention period and are in the medication-free follow up phase. There were no cutaneous or non-cutaneous adverse experiences during the past year; therefore, no drug modifications were required. Benefits to the subjects are pending the completion of the research protocol. The unused investigational drugs are forwarded to the Clinical Drug Respiratory for NCI.

CONCLUSIONS

No conclusions have been determined to date.

REPORT DATE: 05/15/89

WORK UNIT # 1809

DETAIL SUMMARY SHEET

TITLE: Investigation of Photosensitive Reactions to Piroxicam Via Topical Administration and Ultraviolet Light Exposure

KEYWORDS: piroxicam, photosensitivity, drug reaction

PRINCIPAL INVESTIGATOR: James, William LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Dermatology Service

STATUS: Ongoing  
APPROVAL DATE: Jul 1984

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

This study is being done to define the ability of topically applied piroxicam ointment plus UV light to reproduce photosensitive drug eruptions.

TECHNICAL APPROACH

Once a patient is identified clinically as a probable reactor to piroxicam, photo patch testing using UVB and UVA alone and UVB and UVA with drug is accomplished.

PRIOR AND CURRENT PROGRESS

To date seven patients have been tested. Three of the seven had positive photo patch tests reactions to UVA and piroxicam.

CONCLUSIONS

Approximately 50 percent of those tested have manifested photosensitivity to topical drug plan challenge. This may be a useful approach to confirm allergy without systemic challenge.

REPORT DATE: 01/14/89

WORK UNIT # 1300-88

DETAIL SUMMARY SHEET

TITLE: Postoperative Evaluation of Patients with Differentiated Thyroid  
Cancer: A Study Comparing 131I, 201Tl and Magnetic Resonance Imaging  
(MRI)

KEYWORDS: cancer, thyroid

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC  
ASSOCIATES: Wartofsky, Leonard

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: Jan 1988

FUNDING: Current FY: \$ 2,400 Previous FYs: \$ 0 Total: \$ 2,400

STUDY OBJECTIVE

To determine if thallium can be used as an effective nuclide in thyroid cancer patients.

TECHNICAL APPROACH

Patients with known thyroid cancer who are having thyroid scans for their routine care will also have an MRI and a thallium scan. These tests are compared to those results from Iodine 131 scans to determine if thallium is an effective agent.

PRIOR AND CURRENT PROGRESS

Fifteen patients have been studied thus far and there are very interesting results in that most patients have concordance of their scans. However, we have seen several subjects who have had a normal Iodine scan but an abnormal thallium scan and the latter scan did indeed detect thyroid cancer masses or metastases.

CONCLUSIONS

Thus far, thallium seems to be an effective scanning agent in the diagnosis of thyroid cancer.

REPORT DATE: 03/01/89

WORK UNIT # 1301-88

DETAIL SUMMARY SHEET

TITLE: Atrial Natriuretic Peptide (ANP) Effect on Thyroid Function and Growth  
in Porcine and Ovine Cultured Thyrocytes and Intact Rats

KEYWORDS: atrial natriuretic pep, thyroid, porcine

PRINCIPAL INVESTIGATOR: Ahmann, Andrew MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: Mar 1988

FUNDING: Current FY: \$ 3,653 Previous FYs: \$ 0 Total: \$ 3,653

STUDY OBJECTIVE

To evaluate the specific binding of ANP to thyroid cells of various species. To assess the effect of ANP on thyroid cell function in an animal model.

TECHNICAL APPROACH

Primary cell cultures are obtained from procine thyroid of animals sacrificed following surgical experiments at WRAIR. These cells have been studied for  $^{125}\text{I}$ -ANP binding in various aged animals. Likewise ANP binding is studied in porcine and rat thyroid cell membrane preparations. Finally, in porcine cell cultures, the cell responses to ANP have been studied looking at cAMP, cGMP,  $^{3}\text{H}$ - thymidine incorporation and  $^{125}\text{I}$  uptake. Attempts are also being made to develop primary cell cultures of rat thyroid.

PRIOR AND CURRENT PROGRESS

ANP binding is consistently demonstrated for adult Yorkshire pig thyroid cells but is not significant in neonatal pig thyroid. ANP does not stimulate  $^{3}\text{H}$ -thymidine incorporation. Furthermore, we have not been able to demonstrate significant MP production in these cell cultures. ANP does not bind to rat thyroid membranes. Therfore, rat infusions have not been studied. Attempts at rat thyroid cell primary culture have been unsuccessful. The ANP binding in porcine thyroid is reduced in cultured cells by TSH. This is not seen when thyroid membrane is used to look for binding.

CONCLUSIONS

ANP does bind to porcine thyroid as it does to human thyroid cells. This binding is reduced by TSH in vitro. In porcine cells, ANP has not been demonstrated to influence cell growth, cGMP production or  $^{125}\text{I}$  uptake thus far. It seems important to develop an in vivo model in an animal where binding is shown in vitro.

REPORT DATE: 02/14/89

WORK UNIT # 1302-88

DETAIL SUMMARY SHEET

TITLE: Cholestyramine Treatment of Thyrotoxicosis

KEYWORDS: cholestyramine, thyroid

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC

ASSOCIATES: Solomon, Barbara; Wartofsky, Leonard COL MC

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Endocrine-Metabolic Service

APPROVAL DATE: Mar 1988

FUNDING: Current FY: \$14,231 Previous FYs: \$ 0 Total: \$ 14,231

STUDY OBJECTIVE

To investigate the use of oral cholestyramine as a safe and rapid method of lowering serum thyroxine levels in hyperthyroid patients.

TECHNICAL APPROACH

We use a randomized cross over placebo controlled trial. We plan on studying 10-20 patients who will be divided into Group A and Group B. The former have mild thyrotoxicosis and the latter have moderate or severe disease. Group A subjects will be randomized to get either placebo or Questran 4 grams qid. They take the first medication for 14 days, have a 7 day rest period and then take the alternative drug for 14 days. Serum thyroid function tests are measured every several days. Group B subjects are treated the same but also take Tapazole throughout the study.

PRIOR AND CURRENT PROGRESS

We have completed studies on 2 patients and are starting to treat the third at this time. One of the completed patients values are subject to question because of compliance problems. The other patients T4 and T3 levels dropped quite remarkably during the study. The third patient who will start the study in February 1989 is a patient who has had anorexia nervosa in the past and is still being followed by a civilian Psychiatrist. In my view she is capable of giving informed consent and she was presented to a thyroid conference where this view was supported. Her civilian Psychiatrist has been contacted and agrees with this view and the case has been presented to Dr. Dederian who using the data supplied, agrees with this opinion. The patient is capable of handling her own financial affairs, etc. Further, the anorexia nervosa which she had in the past should not interfere with the scientific aspects or interpretation of this study.

CONCLUSIONS

None yet as more patients are required for study.

REPORT DATE: 02/14/89

WORK UNIT # 1303-88

DETAIL SUMMARY SHEET

TITLE: The Clinical Application of In Situ Hybridization to Detect Viral Genomes and Oncogenes in Diseases of the Thyroid and Selected Viral Infections

KEYWORDS: virus, thyroid

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: Apr 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To use newer viral probes to determine if various thyroid tissues contain sequences complementary to these probes. In this manner, we shall determine if viral agents cause or aggravate thyroid disorders.

TECHNICAL APPROACH

We shall use both Southern blots and in situ hybridization with viral probes to examine the presence of viral elements in thyroid glands from patients with various disorders. Our probes are purchased from commercial sources, or are given to use by investigators. We have at present HIV probes, retroviral GAG probes, mos, ras and other oncogene and viral probes.

PRIOR AND CURRENT PROGRESS

We have now performed preliminary Southern blots showing that our techniques are valid. We are now starting to perform Southern blots with the probes mentioned above and in the protocol. We plan on doing Southern blots first and then following up these studies with In situ hybridization studies.

CONCLUSIONS

None yet.

REPORT DATE: 03/07/89

WORK UNIT # 1304-88

DETAIL SUMMARY SHEET

TITLE: The Relationship Between Appraisal Processes and Coping in Middle-Aged Persons with Non-insulin Dependent Diabetes Mellitus

KEYWORDS: appraisal processes, coping strategies, glycemic control

PRINCIPAL INVESTIGATOR: Solomon, Barbara DAC

ASSOCIATES: Shahinpour, Neyereh MSN RN

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Completed  
APPROVAL DATE: Apr 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

a) to describe the relationship between appraisal processes and coping strategies that are reported by middle-aged persons with NIDDM who are dealing with stressful situations related to their illness; and b) to compare the coping strategies of persons with NIDDM in "good glycemic control" and those in "poor glycemic control".

TECHNICAL APPROACH

Patients who met the study criteria were identified and approached by the associate investigator. Those who agreed to participate were asked to sign a consent form. The following study questionnaires were administered by the associate investigator: 1) the Personal Information form; 2) Primary Appraisal; 3) Secondary Appraisal; and 4) Coping Strategies. A 5 ml blood sample for glycosylated hemoglobin (GBH) was obtained after the subjects completed the study questionnaires.

PRIOR AND CURRENT PROGRESS

Subjects were recruited from WRAMC and Veteran Administration Medical Center (VAMC), Washington D.C. WRAMC: 7 subjects who met the study criteria were contacted. Four participated in the study and three refused. VAMC: 70 subjects have been interviewed and 20 subjects who have agreed to participate in the study will be interviewed by mid-May 1989. All blood samples have been analyzed at WRAMC. The associate investigator has been responsible for tracking up samples and delivery of samples from VAMC to WRAMC. The associate investigator will be responsible for the payment of VAMC samples (N=90) to WRAMC laboratory department (diagnostic immunology).

CONCLUSIONS

Data analyses will be performed upon the completion of data collection. This study is closed.

REPORT DATE: 04/24/89

WORK UNIT # 1305-88

DETAIL SUMMARY SHEET

TITLE: A Comparison of the Health, Risk and Physical Performance of Overweight and Normal Weight Soliders

KEYWORDS: overweight, health risks

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC  
ASSOCIATES: Troumbley, Patricia LTC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Completed  
APPROVAL DATE: May 1988

FUNDING: Current FY: \$10,400 Previous FYs: \$ 0 Total: \$ 10,400

STUDY OBJECTIVE

This study was undertaken to assess the validity of the assumptions underlying the Army's Weight Control Program. The purpose of the study was to determine whether overweight and normal weight soldiers differed with respect to health risk, self-motivation, psychological symptomatic distress, health status, and physical fitness.

TECHNICAL APPROACH

A comparative study was planned. A designation of overweight (soldiers enrolled in the Army's Weight Control Program) was the primary independent variable. The Interaction Model of Client Health/Behavior and empirical literature about the causes and effects of overweight/obesity were used. The overall hypothesis was that overweight and normal weight groups of soldiers, matched with respect to gender, rank and unit would not differ with respect to health risk (scores in the US Army's Wellness Check, version 2.0); self-motivation (score on Dishman and Ickes' self-motivation inventory); psychological symptomatic distress (scores in Decogatis' Brief Symptom Inventory); health status (score on Duke-UMC Profile).

PRIOR AND CURRENT PROGRESS

The sample consisted of 154 active duty male and female enlisted Army soldiers assigned to the Maryland/District of Washington area. There were two subsamples. One group was composed of 77 overweight soldiers enrolled in the Army's Weight Control Program. The other was composed of 77 normal weight soldiers randomly selected from a gender-stratified unit-specific list. To test the hypothesis, data were analyzed using multivariate analysis of variance (MANOVA).

CONCLUSIONS

Findings indicated that the overweight and normal weight soldier differed, with the former having greater health risk, poorer health status, and lower physical fitness test scores. The two groups did not differ in self-motivation or psychological symptomatic distress.

REPORT DATE: 05/01/89

WORK UNIT # 1306-88

DETAIL SUMMARY SHEET

TITLE: Predicting Energy Requirements in Women with Gestational Diabetes Mellitus (GDM)

KEYWORDS: energy, requirement, gestational diabetes

PRINCIPAL INVESTIGATOR: Coffey, Lauri CPT SP

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: May 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

This study compares various methods of calculating or predicting energy expenditure in women with gestational diabetes mellitus. Indirect calorimetry will serve as the gold standard.

TECHNICAL APPROACH

Thirty females with gestational diabetes (Group A) will be recruited for the study. (Group B) All pregnant women will be measured during the third trimester indirect calorimetry, dietary history, anthropometric measures will be secured for each patient. Regression analysis will be utilized to analyze the data.

PRIOR AND CURRENT PROGRESS

Ten patients have been recruited for Group A, 2 patients for Group B. There have been no adverse reaction or direct benefits to patients scheduled.

CONCLUSIONS

Since the study is still ongoing it is premature to offer definitive conclusions.

REPORT DATE: 01/23/90

WORK UNIT # 1307-88

DETAIL SUMMARY SHEET

TITLE: Studies of the Genome of Patients with Thyroid Hormone Resistance

KEYWORDS:

PRINCIPAL INVESTIGATOR: Fein, Henry LTC MC

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Endocrine-Metabolic Service

APPROVAL DATE: Sep 1988

FUNDING: Current FY: \$ 596 Previous FYs: \$ 0 Total: \$ 596

STUDY OBJECTIVE

Data unavailable at the time of publication.

TECHNICAL APPROACH

Data unavailable at the time of publication.

PRIOR AND CURRENT PROGRESS

Data unavailable at the time of publication.

CONCLUSIONS

Data unavailable at the time of publication.

REPORT DATE: 05/17/89

WORK UNIT # 1323-80

DETAIL SUMMARY SHEET

TITLE: Thyrotropin (TSH) Receptors in Human Thyroid Tissue

KEYWORDS: hyrotropin, human, tissue

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC

ASSOCIATES: Latham, Keith; Lukes, Yvonne; Wartofsky, Leonard

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Endocrine-Metabolic Service

APPROVAL DATE: Jul 1980

FUNDING: Current FY: \$22,576 Previous FYs: \$ 83,629 Total: \$ 106,205

STUDY OBJECTIVE

a) To measure TSH, microsomal, thyroglobulin and beta receptors in thyroid tissue from various groups of patients with Graves' disease patients, normal tissue and in patients with non-toxic goiter; b) to utilize TSH receptors to measure thyroid stimulating proteins in Graves' disease and autoimmune disease; c) to measure and compare specific T and B cell responses in thyroid glands and to isolate and fuse the thyroid gland cells to make specific hybridomas.

TECHNICAL APPROACH

TSH receptors and other receptors are isolated from the thyroid gland by standard techniques including isolating other receptors with a specific solubilizing detergent. TSH receptors are then determined by assessing binding to  $^{125}$ I TSH and other receptors are determined by specific binding on ELISA plates. Specific cells in autoimmune thyroid glands are determined by staining techniques or by FACS sorter. Thyroid cells are cultured, clones are prepared, and hybridomas are prepared by standard techniques.

PRIOR AND CURRENT PROGRESS

We have identified and stained the localization of specific T and B cells within the thyroid gland and have found a lack of suppressor T cells and an abundance of helper T cells. We have developed new assays to measure thyroid-stimulating growth immunoglobulins and thyroid-stimulating immunoglobulins by uptake into thyroid tissue. We have developed antibodies against these TSH receptors that are blocking formation which is elevated in these diseases. We have determined that the thyroid sites are HLA positive. We have measured oncogene expression in normal thyrocytes, cancer and nodular thyrocytes and in thyrocytes from patients autoimmune disease. There is no difference in c-myc expression in these thyrocytes. In the process of measuring other oncogene expression (e.g. EGFT). We are trying to clone the gene for the TSH receptor. We have produced a monoclonal antibody which can recognize the TSH receptor.

CONCLUSIONS

We have obtained evidence that intra-thyroidal lymphocytes are the main cause of autoimmune thyroid disease and that they are the initiating factor in these autoimmune thyroid diseases. Further, we have utilized tissue to obtain TSH receptors. We are extending these studies to measure messenger RNA from these various tissues and to look for abnormal translated proteins, and enhanced oncogene expression.

REPORT DATE: 06/02/89

WORK UNIT # 1330-81

DETAIL SUMMARY SHEET

TITLE: Utilization of Hybridoma Antibodies as a Physiologic Probe of Thyrotropin (TSH) Action

KEYWORDS: hybridoma, physiologic, thyrotropin

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC

ASSOCIATES: Carr, Frances PhD; Wartofsky, Leonard COL MC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Completed  
APPROVAL DATE: Jul 1981

FUNDING: Current FY: \$15,400 Previous FYs: \$ 0 Total: \$ 15,400

STUDY OBJECTIVE

To develop hybridoma monoclonal antibodies and use them as specific probes of thyroid hormone action and TSH receptor action to help understand the causes and aggravating factors of autoimmune thyroid disease.

TECHNICAL APPROACH

Specific monoclonal antibodies are made by standard hybridoma techniques. We either utilize human-human or human-mouse hybridoma techniques. These either involve injecting specific antigens into mice and utilizing the B cell formed and fusing them with a human myeloma line or EB virus transformation of intra-thyroidal or peripheral B cells with subsequent fusion to human partners. Specific antibodies are determined by measuring binding on ELISA plates.

PRIOR AND CURRENT PROGRESS

We have made significant progress in this protocol and have made antibodies against various factors to include: a) TSH receptor; b) TSH receptor antibodies; c) thyroglobulin; d) microsomal antigen components of thyroid tissue. We have utilized these hybridoma antibodies to study TSH receptor action. In addition, we have used antibodies to try to screen a cDNA thyroid library in order to clone the TSH receptor or unique autoantigens. We have identified a set of antibodies that recognize unique proteins and are presumably related to histones. We have proven heterogeneity of response to intrathyroidal lymphocytes from patients with autoimmune thyroid disease. Dr. Baker will continue to collaborate at the University of Michigan.

CONCLUSIONS

Hybridoma antibodies can be used as specific probes of receptor action.

REPORT DATE: 12/22/88

WORK UNIT # 1338-82

DETAIL SUMMARY SHEET

TITLE: Membrane Receptors in Peripheral Circulating Mononuclear Cells

KEYWORDS: beta receptors, peripheral, mononuclear cells

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Endocrine-Metabolic Service

APPROVAL DATE: Feb 1982

FUNDING: Current FY: \$ 5,998 Previous FYs: \$ 4 Total: \$ 6,002

STUDY OBJECTIVE

To measure hormone receptors in the membranes of peripheral circulating mononuclear cells.

TECHNICAL APPROACH

TSH receptors are measured by labeling I-125 TSH with unlabeled TSH to derive a Scatchard analysis. Other hormone receptors such as Beta Adrenergic alpha-adrenergic, T3 and T4 receptors are also identified, as are lymphokine receptors, such as IL2.

PRIOR AND CURRENT PROGRESS

We have been successful in measuring membrane receptors to TSH and Beta Adrenergic hormones. We have noticed that Beta Adrenergic receptors are altered during various physiologic states such as underfeeding and when patients are ill. We now have the ability to measure alpha-adrenergic receptors, and we will identify the receptor number for alpha and beta receptor cells of patients with systemic illnesses. This research has been difficult to complete because of technical problems in setting up an alpha receptor assay for platelets; we believe these problems have now been solved. Thirty patients have been studied.

CONCLUSIONS

ALPHA receptors are present in platelet membranes.

REPORT DATE: 12/22/88

WORK UNIT # 1339-82

DETAIL SUMMARY SHEET

TITLE: Immunology of Thyroid Disease

KEYWORDS: immunology, thyroid, disease

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC  
ASSOCIATES: Baker, James MAJ MC; Tseng, Y PhD

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: Feb 1982

FUNDING: Current FY: \$ 9,800 Previous FYs: \$ 3,024 Total: \$ 12,824

STUDY OBJECTIVE

To culture human thyrocytes and to determine if thyroid membrane TSH receptors are present in these thyrocytes. Secondly, to study the wide variety of antibody responses that are found in patients with Graves' disease.

TECHNICAL APPROACH

Thyrocytes are obtained at the time of surgery and are isolated by digestion and then separated by Ficoll-Hypaque. The thyrocytes are cultured and then are either grown by themselves or in the presence of antigen presenting cells; they may be fused to myeloma fusion partners. The T cells and B cells can be activated by mitogens, as well as by specific antigens, and the antibodies that are formed can be isolated and purified.

PRIOR AND CURRENT PROGRESS

1) We have shown that TSH receptors and Beta Adrenergic receptors reside in the thyroid gland. 2) We have demonstrated that we can obtain a relatively pure population of thyrocytes which can be used to stimulate peripheral blood cells with patients with Graves' disease. It is the antigens and the HLA-DR phenotype of the thyrocytes that seem to be capable of causing the stimulation. 3) We have also isolated a wide variety of antibodies from patients with Graves' disease, some of which are inhibitory and some of which are stimulatory with regard to CAMP. 4) We have also been successful in other aspects of the study which is measuring TSH receptors in a wide variety of bacteria and unicellular organisms to include Mycoplasma, Yersinia, and Leischmania. Further, patients with Graves' disease have antibodies directed against these various unicellular organisms. 5) Identified new intracellular auto antigens, trying to isolate and characterize.

CONCLUSIONS

1) TSH receptor and Beta-Adrenergic receptors are present in thyroid tissue from Graves' patients. 2) Hashimoto's thyroiditis and Graves' disease are secondarily caused by heterogeneous polyclonal activation of B cells in a secondary fashion. 3) There is a wide homology across interspecies lines in regard to hormone receptors. TSH receptors are found in unicellular organisms and may play a role in the pathogenicity of these organisms.

REPORT DATE: 10/05/88

WORK UNIT # 1349-84

DETAIL SUMMARY SHEET

TITLE: Immunoglobulin Production in Thyroid Disease

KEYWORDS: immunoglobulin, production, thyroid

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC

ASSOCIATES: Wartofsky, Leonard COL MC; Baker, James MAJ MC

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Endocrine-Metabolic Service

APPROVAL DATE: Nov 1983

FUNDING: Current FY: \$17,634 Previous FYs: \$ 837 Total: \$ 18,471

STUDY OBJECTIVE

To a) document the presence and frequency of anti-receptor antibodies in patients with autoimmune thyroid disease; b) culture lymphocytes of patients with autoimmune thyroid disease and measure the specific antibodies generated; c) document the presence and frequency of anti-idiotypic antibodies in these diseases; d) document and measure the frequency of immune complexes; e) to generate anti-receptor and anti-idiotypic antibodies in animals.

TECHNICAL APPROACH

Use Elisa techniques to measure specific antibodies against TSH, TSH receptor or thyroglobulin. Lymphocytes are isolated on Ficoll-Hypaque by separation procedures, and specific antibodies are measured by Elisa immune complex or measured by specific binding to C3B by Elisa.

PRIOR AND CURRENT PROGRESS

We have determined that approximately 20% of patients with autoimmune thyroid disease have circulating antibodies against insulin and circulating antibodies against TSH. We believe each of these antibodies are anti-idiotypic in nature. In addition, we have isolated intrathyroidal B cells from several patients and have determined that B cells are capable of making a wide variety of antibodies against TSH receptor, TSH, insulin, Beta receptor and microsome as well as TSH receptor antibody. In addition, we have utilized a C3B binding assay to measure that immune complexes occur in about 50% of patients with Graves' disease and further, we have disrupted these immune complexes to indicate that there are TSH binding anti-idiotypes and TSH receptor antibodies combined in some of these immune complexes. This has important implications with regard to modification of disease activity in Graves' disease. No adverse reactions in all 65 patients.

CONCLUSIONS

Autoimmune thyroid disease is a wide-ranging disease in which a panoply of antibodies are formed, not just against TSH receptor, but against TSH, microsome, thyroglobulin, insulin and beta receptors.

REPORT DATE: 01/12/89

WORK UNIT # 1351-84

DETAIL SUMMARY SHEET

TITLE: Cyclosporin Treatment of Graves' Ophthalmopathy

KEYWORDS: cyclosporine, exophthalmos, Graves' disease

PRINCIPAL INVESTIGATOR: Wartofsky, Leonard COL MC

ASSOCIATES: Ahmann, Andrew MAJ MC; LaPiana, Francis COL MC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: Jan 1984

FUNDING: Current FY: \$ 0 Previous FYs: \$ 538 Total: \$ 538

STUDY OBJECTIVE

To assess the effectiveness of cyclosporine in the treatment of severe Graves' ophthalmopathy.

TECHNICAL APPROACH

Patients with severe Graves' ophthalmopathy demonstrating some progression in the prior year are randomized to receiving cyclosporine or high dose prednisone for three weeks. There is then a three week rest period before crossover to the alternative drug for three weeks. Objective improvement is assessed by measurement of proptosis, tonometry, the ATA ophthalmopathy index and serial orbital CT scans.

PRIOR AND CURRENT PROGRESS

In this multicenter study involving all US Army medical centers, a total of 5 patients have completed the protocol. At WRAMC, 3 patients have enrolled, but only 2 patients have completed the protocol. The other patient dropped out after 10 days of Prednisone due to intolerable gastrointestinal side effects. He did not receive Cyclosporine. Our patients receiving Cyclosporine had no significant or unexpected side effects. They experienced improvement in soft tissue findings but no decrease in proptosis. Cyclosporine showed no therapeutic advantage over Prednisone except for better patient tolerance. No patient has received Cyclosporine on protocol in the last year.

CONCLUSIONS

The projected number of study patients has not been realized, and insufficient data have been generated to make valid statistical comment. We believe the study deserves extension. We are going to submit one last formal reminder to collaborating endocrinologists in the Army, requesting consideration of appropriate patients for the protocol.

REPORT DATE: 02/12/89

WORK UNIT # 1353-84

DETAIL SUMMARY SHEET

TITLE: Effect of Short Term Fasting on Immunity

KEYWORDS: immunity, fasting

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC

ASSOCIATES: Baker, James MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: Mar 1984

FUNDING: Current FY: \$ 0 Previous FYs: \$ 6,800 Total: \$ 6,800

STUDY OBJECTIVE

To determine if immunologic responses are altered during short-term fasting.

TECHNICAL APPROACH

Overweight patients are placed on a 5 day regular calorie diet and then a 15 day low calorie diet (generally, less than 500 calories). On the last day of the fed period and the last day of the fasting period, patients have blood drawn and mononuclear cells isolated on Ficoll-Hypaque gradients. Once these lymphocytes are isolated, approximately 200,000 cells are placed into vials in the presence of absence of mitogens such as PHA or Pokeweed mitogen. The ability of these mitogens to cause tritiated-thymidine stimulation in these white cells is noted, and the production of interleukin is noted in the supernatants of these patients.

PRIOR AND CURRENT PROGRESS

We have noted that there is not a uniform response by patients during the underfeeding state. Ability to form IL2 seems to be slightly inhibited, however, the responses of tritiated thymidine appear normal, as do the responses of various mitogens.

CONCLUSIONS

Underfeeding is a heterogeneous immunologic state in which some responses are decreased and other responses are normal or enhanced. We plan on extending these studies to examine different times of incubation of their white cells. Fifteen patients have been started. We have lost technical help preventing us from finding this project over the last year. We also have had a nursing shortage on Ward 47 and this ward has had to close.

REPORT DATE: 03/03/89

WORK UNIT # 1354-84

DETAIL SUMMARY SHEET

TITLE: Prolonged TRH Infusions in Graves' Disease

KEYWORDS: TRH, TSH, Graves' disease

PRINCIPAL INVESTIGATOR: Wartofsky, Leonard COL MC

ASSOCIATES: Ahmann, Andres MAJ MC; Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine

STATUS: Completed

SERVICE: Endocrine-Metabolic Service

APPROVAL DATE: Mar 1984

FUNDING: Current FY: \$ 9,868 Previous FYs: \$ 7,924 Total: \$ 17,792

STUDY OBJECTIVE

To elucidate the mechanism of reduced TSH production in treated patients with Graves' disease who maintain low serum TSH despite apparent hypothyroidism.

TECHNICAL APPROACH

Treated Graves' patients with low/normal T4 and low serum TSH will be compared to suppressed thyroid CA patients in regard to their responses to bolus TRH and prolonged TRH infusion. The data should help determine whether the refractoriness to TRH stimulation is due to chronic hypothalamic suppression. The Graves' patients will also be given ipodate to block intrapituitary T4 to T3 conversion to assess its role in refractoriness to TRH stimulation.

PRIOR AND CURRENT PROGRESS

We have not treated any patients in the past several years. This protocol has not been active due to recruiting difficulties and the nonavailability of clinical facilities to accomodate these patients on short notice for complex testing. The significance of this study in its original form has been reduced due to the availability of supersensitive TSH assays commercially.

CONCLUSIONS

This protocol has been terminated. A new protocol with modifications will be submitted if deemed appropriate.

REPORT DATE: 02/14/89

WORK UNIT # 1355-84

DETAIL SUMMARY SHEET

TITLE: Thyroid Disease in the Elderly

KEYWORDS: thyroid disease, elderly

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC

ASSOCIATES: Wartofsky, Leonard COL MC; Crantz, Joan MD

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Endocrine-Metabolic Service

APPROVAL DATE: Apr 1984

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To measure the frequency of thyroid abnormalities in the elderly.

TECHNICAL APPROACH

Patients at the U.S. Soldiers and Sailors Home are screened by measuring T4, T3 and TSH by radioimmunoassays.

PRIOR AND CURRENT PROGRESS

About 300 patients at the U.S. Soldiers and Sailors Home have been screened for thyroid abnormalities. Several hundred individuals have been screened, and the incidence of elevated TSH is approximately 15%, and the incidence of clinical hypothyroidism with low T4 and high TSH is approximately 5%. Most of these individuals did not realize they were hypothyroid, and repeat evaluations have been obtained on these individuals. The majority confirm the original evaluation. This very high frequency of hypothyroidism is surprising and has great clinical implications. We have communicated with the primary care physicians at the institution who are giving appropriate clinical follow-up on all of these patients. We shall extend this study to more individuals and perform some of the subsets that have been approved, including giving iodine.

CONCLUSIONS

Hypothyroidism is very common in the elderly and such patients need to be screened routinely.

REPORT DATE: 05/16/89

WORK UNIT # 1356-84

DETAIL SUMMARY SHEET

TITLE: Ketoconazole-Induced Suppression of Serum Testosterone Levels in Men

KEYWORDS: ketoconazole, testosterone, gonadotropins

PRINCIPAL INVESTIGATOR: Glass, Allan LTC MC

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Endocrine-Metabolic Service

APPROVAL DATE: Jul 1984

FUNDING: Current FY: \$ 498 Previous FYs: \$ 3,854 Total: \$ 4,352

STUDY OBJECTIVE

To determine whether the stimulation of serum LH and FSH which follows the ketoconazole-induced reduction in serum testosterone will be useful as a test of pituitary gonadotropin reserve.

TECHNICAL APPROACH

Subjects are given ketoconazole 200mg every eight hours for seven days, and serum LH, FSH, testosterone, and 17-OH-progesterone are measured before and after drug administration.

PRIOR AND CURRENT PROGRESS

No patients have been studied under this protocol in the past year. This has been due primarily to the nursing shortage and the closure of the Kyle Metabolic Unit, with lack of ability to perform outpatient research tests. It is hoped that with the imminent re-opening of the Kyle Metabolic Unit ward, it will be possible to resume work on this protocol.

CONCLUSIONS

As previously published, ketoconazole reduces serum testosterone and increases serum LH and FSH in a dose-dependent fashion. The effect of ketoconazole on LH and FSH in patients with hypothalamic-pituitary disorders remains to be seen.

REPORT DATE: 12/22/88

WORK UNIT # 1359-85

DETAIL SUMMARY SHEET

TITLE: Newer Investigations into the Immune Mechanisms of Thyroid Disease  
(1985)

KEYWORDS: immunology, thyroid disease

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC  
ASSOCIATES: Baker, James MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: Feb 1985

FUNDING: Current FY: \$ 4,163 Previous FYs: \$ 40,273 Total: \$ 44,436

STUDY OBJECTIVE

To define the T and B cell abnormalities in patients with thyroid disease, both in the peripheral mononuclear cells, as well as in the intra-thyroidal mononuclear cells.

TECHNICAL APPROACH

There are various aspects of this study: 1) Peripheral mononuclear cells are isolated by Ficoll-Hypaque and the lymphocytes obtained are identified by fluorescent staining and are cultured in the presence of various mitogens. Our aim is to derive an antigen specific T cell population. 2) Perform similar studies with the intra-thyroidal lymphocytes. 3) Genes encoding for the T cell receptor that are antigen specific will be characterized. This is performed by isolating the messenger RNA from the peripheral cells' cytoplasm of the DNA from the nucleus. The DNA, so obtained, is broken up by restriction endonucleases and is then subjected to electrophoresis.

PRIOR AND CURRENT PROGRESS

We have been successful in many aspects of this study. 1) We have isolated clones against thyroid membrane antigens that are unique to patients with Graves' disease. 2) We have shown by peripheral stimulation that intra-thyroidal and peripheral T cells are in various stages of activation compared to normal subjects' white cells. 3) We have been successful in making hybridoma antibodies directed against thyroid membrane that are capable of enhancing TSH action in the FRTL5 cell lines. We have set up a specific IL2 assay and are now performing T cell fusion studies to help study T cell receptor. 4) We have identified the specific expressions of RNA encoding for various oncogenes in white cells and thyrocytes. 5) We have identified translated proteins in the thyrocytes of patients with various disorders. Thirty patients have been studied.

CONCLUSIONS

Graves' disease is an autoimmune disease in which there is a heterogeneous activation of T and B cells; the cause of Graves' disease, at present, is thought to be cell hybridomas, B cell clones, B cell hybridomas, and study of antigen presentation. We shall also continue to identify mRNA and DNA that encode for proteins or receptors of interest. We shall use reticulocyte lysate systems for expression of mRNA and will use phage or plasmid vector for DNA expression.

REPORT DATE: 07/10/89

WORK UNIT # 1361-85

DETAIL SUMMARY SHEET

TITLE: 1,25-Dihydroxyvitamin D Action at the Nuclear Level

KEYWORDS: 1,25-Dihydroxyvitamin D, liver, endocrine

PRINCIPAL INVESTIGATOR: Duncan, William LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: May 1985

FUNDING: Current FY: \$ 0 Previous FYs: \$ 79,217 Total: \$ 79,217

STUDY OBJECTIVE

To identify proteins synthesized by the liver in response to 1,25(OH) 2D3 treatment.

TECHNICAL APPROACH

The technique of differential hybridization will be used to enrich the poly A-mRNA prior to cell free translation.

PRIOR AND CURRENT PROGRESS

Techniques to conduct this research protocol have been developed to include isolation of hepatic mRNA and Northern analysis, and vitamin D deficient rats have been raised for the first time at WRAMC. Isolation of unique mRNA's from vitamin D sufficient rats is underway.

CONCLUSIONS

This protocol is central to our effort to understand the molecular basis of vitamin D action.

REPORT DATE: 07/10/89

WORK UNIT # 1363-85

DETAIL SUMMARY SHEET

TITLE: 1,25-Dihydroxyvitamin D Receptors in Liver and Skeletal Muscle

KEYWORDS: 1,25-dihydroxyvitamin D, liver, muscle

PRINCIPAL INVESTIGATOR: Duncan, William LTC MC

ASSOCIATES: Wray, Linton COL MC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: Jul 1985

FUNDING: Current FY: \$ 6,841 Previous FYs: \$ 6,559 Total: \$ 13,400

STUDY OBJECTIVE

To identify 1,25(OH)2D<sub>3</sub> receptors in rat liver and to study the regulation of this receptor.

TECHNICAL APPROACH

Standard biochemical techniques for identification are employed after isolation of rat liver nuclei.

PRIOR AND CURRENT PROGRESS

The 1,25(OH)2D<sub>3</sub> receptor has been identified and characterized in rat liver nuclei. This receptor has been identified in skeletal muscles, so no further work has been done by us in muscle. We have studied the hormonal regulation of this receptor and have found differences in its regulation in different tissues.

CONCLUSIONS

The vitamin D receptor is present in liver and is regulated by several hormones in an organ specific manner.

REPORT DATE: 08/16/89

WORK UNIT # 1366-85

DETAIL SUMMARY SHEET

TITLE: Pancreatic Islet Transplantation Across Major Histocompatibility Barriers

KEYWORDS: pancreas, transplantation, islets

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC  
ASSOCIATES: Baker, James MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Completed  
APPROVAL DATE: Sep 1985

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

a) Isolate and grow pancreatic islet cells in tissue culture. Determine the extent of pancreatic islet cells antigenicity by determining their ability to act as foreign proteins and to stimulate human white cells to proliferate; b) to alter the recognized antigenicity of the pancreatic islet cells by exposing them to immunosuppressive agents; c) to transplant islet cells into diabetic mice or rats in order to treat their diabetes.

TECHNICAL APPROACH

Customary isolation of islets - Pancreatic tissues are digested with collagenase with a modified digestion-filtration method. The islets are hand-picked under a dissection microscope. Contaminating acinar tissues and blood vessels are removed form the islets by the single layer hypaque-ficoll separation technique. Islets collected at the interface are repicked under dissection microscope and then washed with Hank's balanced salt solution (HBSS) prior to transplantation or in vitro culture. Islets are cultured at 37 degree C in culture medium (M199 supplemented with 15% feta calf serum, 100 U/ml penicillin, 100 ug/ml streptomycin, 1.5 mg/ml glucose) in a humidified 5% CO<sub>2</sub> incubator.

PRIOR AND CURRENT PROGRESS

Unfortunately, there have been no personnel available for assignment to this project and no significant progress has been made. As a result, I would ask that it be terminated and if further personnel become available, I will initiate a new protocol.

CONCLUSIONS

Much further study is required. This project is hampered by the transfer of Dr. Vic Modesto.

REPORT DATE: 04/18/89

WORK UNIT # 1367-86

DETAIL SUMMARY SHEET

TITLE: Modification of Diabetogenic Effects of Pentamadine

KEYWORDS: modification, diabetogenic, pentamadine

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine

SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing

APPROVAL DATE: Oct 1985

FUNDING: Current FY: \$ 7,014 Previous FYs: \$ 167 Total: \$ 7,181

STUDY OBJECTIVE

To determine the effects of Pentamadine on serum glucose and insulin and pancreatic insulin in rats injected with this agent.

TECHNICAL APPROACH

Male rats weighing 150-250 grams are obtained and placed on water ad lib throughout the experiment as noted. Following 5 days of observation, rats are divided into 5 groups. The rats receive daily intraperitoneal injections for 14 days as follows: Group 1-sterile water, Group 2-4 mg per kg of Pentamadine, Group 3-8 mg per kg of Pentamadine, Group 4-16 mg per kg Pentamadine, and Group 5-24 mg per kg Pentamadine. Every 17 hours during the 14 day treatment period, rats are weighed fasted for 2 hours to have blood glucose measured from the tail vein. Following day 14, rats are fasted over night, although they have access to free water. The next morning the rats are weighed.

PRIOR AND CURRENT PROGRESS

Insulin over glucose ratio was 3.4 in the group that received 14 days sterile water and rose to 1.47 in the group that received 24 mg per kg Pentamadine to 1.0 in the groups that received 40 mg per kg Pentamadine. These studies have been repeated with approximately the same results. Preliminary histologic exam of the pancreas indicate an increased insulin content in the pancreas in the Pentamadine treated rats. These results taken together indicate that Pentamadine has a significant effect of lowering insulin secretion and allowing elevated glucose. The mechanism of this result seems to be, although synthesized, the inability of Pentamadine secretion by the pancreas. Further studies are proceeding by repeating these studies and by in vitro culture techniques that Dr. Hays is performing at NAMRI in Bethesda, MD.

CONCLUSIONS

Pentamadine works to inhibit insulin secretion.

REPORT DATE: 08/18/88

WORK UNIT # 1369-86

DETAIL SUMMARY SHEET

TITLE: Magnesium Status and Thyroid Disease

KEYWORDS: magnesium, thyroid, disease

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC  
ASSOCIATES: Dolev, Eran; Deuster, Pat

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: Oct 1985

FUNDING: Current FY: \$ 2,719 Previous FYs: \$ 1,634 Total: \$ 4,353

STUDY OBJECTIVE

To measure magnesium and zinc levels in blood, tissue and urine in control patients and in patients with hyperthyroidism and hypothyroidism.

TECHNICAL APPROACH

Plasma magnesium and zinc, red blood cell magnesium and zinc, mononuclear cell magnesium and zinc content and 24 hour urine excretion of magnesium and zinc were measured. Red blood cell and white blood cell counts were determined on a counter, model ZM and hemoglobin was measured with a counter electronics hemoglobinometer. Whole blood was hemolyzed by dilution with deionized water, vortexed, and then frozen. Plasma for heparinized tubes was separated from whole blood by centrifugation and frozen for later analysis. Mononuclear cells were isolated by ISOLYMPH, with harvesting and counting of the cells followed by lysis with deionized water and ultrasonication to release magnesium and zinc.

PRIOR AND CURRENT PROGRESS

Twenty-five controls, (10 men and 15 women), 11 hyperthyroid and 29 hypothyroid patients volunteered to participate in this study. Magnesium status results indicated that although there was a tendency for patients with hyperthyroidism to have lower plasma concentration of magnesium as compared to hypothyroid and euthyroid subjects, the differences were not significant. Similarly, red blood cell magnesium did not differ between the groups. No significant association between blood cell magnesium and any tests of thyroid function was noted. There was a significant negative correlation between plasma magnesium and resin T3 uptake ( $r = -0.42$ ;  $P$  less than 0.01). In contrast to red blood cell and plasma magnesium, urinary excretion and urinary clearance of magnesium were significantly lower in hypothyroid as compared to both hyperthyroid and euthyroid subjects.

CONCLUSIONS

Plasma magnesium concentrations tended to be lower in hyperthyroid patients, but differences among the groups were not significant. Similarly, red blood cell concentration and mononuclear cell content of magnesium did not differ among the three groups. In contrast, hypothyroid patients showed marked decreases in urinary magnesium excretion as compared to hyperthyroid and euthyroid subjects.

REPORT DATE: 10/27/88

WORK UNIT # 1370-86

DETAIL SUMMARY SHEET

TITLE: Effect of Short Term Fasting on Percent Body Fat as Determined by Skinfold Caliper, Circumference Measurements, Bioelectrical Impedance Measurements, and Hydrostatic Weighing and Energy Balance

KEYWORDS: percent body fat, measurement techniques, body composition

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: Oct 1985

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine the effect of fasting versus consumption of a balanced calorie restricted diet on body fat loss and to compare the accuracy of the bioelectrical impedance measurement technique with the skinfold measurement technique prescribed in AR 600-9, the circumference measurement technique prescribed in the proposed AR 600-9, hydrostatic weighing and energy balance.

TECHNICAL APPROACH

Forty healthy volunteers are assigned to one of 2 groups. One group gets a 10 day very low kcal diet (50); the other group gets a 10 day reasonable low kcal diet (1000-1500). Both groups start with a 4 day maintenance diet and end with a 7 day 500 kcal diet. Each subject is measured 3 times with each of 4 body composition measurement techniques. There are 2 modifications to the original study. Female volunteers are used and the reasonable kcal level was increased.

PRIOR AND CURRENT PROGRESS

During the past year 21 subjects have participated in the study. All patients in the study have lost weight, benefiting them by helping in their attempts to reach Army weight control standards.

CONCLUSIONS

Data collected to date indicate that each of the percent body fat estimation techniques can accurately assess changes in percent body fat as weight is lost. We are continuing to study energy balance in the patients.

REPORT DATE: 09/22/88

WORK UNIT # 1371-86

DETAIL SUMMARY SHEET

TITLE: Transplantation Antigens on Spermatozoa

KEYWORDS: sperm, HLA, antigens

PRINCIPAL INVESTIGATOR: Glass, Allan LTC MC

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Endocrine-Metabolic Service

APPROVAL DATE: Nov 1985

FUNDING: Current FY: \$ 6,958      Previous FYs: \$ 555      Total: \$ 7,513

STUDY OBJECTIVE

To determine the nature and amount of transplantation antigens in spermatazoa.  
To compare transplantation antigens in blood cells and sperm.

TECHNICAL APPROACH

Measurement of HLA antigens on sperm using monoclonal antisera.

PRIOR AND CURRENT PROGRESS

Previous studies using monoclonal antisera and standard immunofluorescent staining techniques have not revealed HLA antigens on sperm surface. However, recent evidence indicates that technical factors may cause these antigens to be lost during processing. Ways around this problem are being explored. In addition, use of molecular biology techniques to help answer these questions is being explored.

CONCLUSIONS

HLA antigens are not present on sperm surface using conventional techniques.

REPORT DATE: 09/22/89

WORK UNIT # 1372-86

DETAIL SUMMARY SHEET

TITLE: Effect of Altered Energy Balance on Sexual Maturation in Rats

KEYWORDS: energy balance, sexual maturation, hyperthyroidism

PRINCIPAL INVESTIGATOR: Glass, Allan LTC MC

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Endocrine-Metabolic Service

APPROVAL DATE: Nov 1985

FUNDING: Current FY: \$ 2,561 Previous FYs: \$ 38,173 Total: \$ 40,734

STUDY OBJECTIVE

To determine the effect of alterations in energy balance on sexual maturation in rats.

TECHNICAL APPROACH

Manipulation of energy balance in rats by food restriction, hyperthyroidism, or catecholamine infusion. Parameters of puberty and growth monitored serially, including assessment of such factors as hormone levels, growth rates, timing of vaginal opening, and sperm production.

PRIOR AND CURRENT PROGRESS

During the past one year, I have been obtaining a token number of animals because WRAIR was on a budget freeze and could no longer order animals. Due to this inability to obtain experimental animals, no research could be carried out.

CONCLUSIONS

Deferred because of lack of recent experimental results (see above).

REPORT DATE: 12/12/88

WORK UNIT # 1373-86

DETAIL SUMMARY SHEET

TITLE: Lymphocyte Subsets in Men with Low Sperm Counts

KEYWORDS: lymphopenia, oligospermia, blood counts

PRINCIPAL INVESTIGATOR: Glass, Allan COL MC

DEPARTMENT: Department of Medicine

STATUS: Completed

SERVICE: Endocrine-Metabolic Service

APPROVAL DATE: Jan 1986

FUNDING: Current FY: \$ 1,662 Previous FYs: \$ 5,432 Total: \$ 7,094

STUDY OBJECTIVE

To determine whether men with low sperm counts have abnormalities in blood cell counts.

TECHNICAL APPROACH

Measurement of blood counts and lymphocyte subsets in oligospermic men and fertile controls.

PRIOR AND CURRENT PROGRESS

CBCs studied retrospectively in 72 male partners of infertile couples and 119 healthy controls. CBCs and lymphocyte subsets studied prospectively in 24 fertile controls and 12 infertile men with oligospermia. All subject recruitment completed; paper published; study completed.

CONCLUSIONS

Lymphopenia noted in retrospective study of infertile men could not be confirmed in prospective study. Red cell and platelet indices, as well as lymphocyte subsets, were normal in infertile men.

REPORT DATE: 02/09/89

WORK UNIT # 1376-86

DETAIL SUMMARY SHEET

TITLE: Ketoconazole Effects on Vitamin D in Hypercalcemic Patients

KEYWORDS: ketoconazole, hypercalcemia, vitamin D

PRINCIPAL INVESTIGATOR: Glass, Allan COL MC

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Endocrine-Metabolic Service

APPROVAL DATE: Apr 1986

FUNDING: Current FY: \$ 157 Previous FYs: \$ 17,766 Total: \$ 17,923

STUDY OBJECTIVE

To determine whether ketoconazole can reduce serum vitamin D levels and/or serum calcium levels in hypercalcemic patients, and to assess whether such reduction might be of diagnostic or therapeutic use.

TECHNICAL APPROACH

Measurement of serum calcium, PTH, vitamin D metabolites in hypercalcemic patients before and after administration of ketocanazole 200 every 8 hours for one week.

PRIOR AND CURRENT PROGRESS

Nine normal subjects studied with various doses of ketconazole. Fifteen subjects with primary hyperparathyroidism studied with ketoconazole 200 mg every 8 hours. One subject each with hypercalcemic sarcoidosis and hypercalcemic lymphoma studied with ketoconazole 200 mg every 8 hours. Two papers were published; one paper was submitted for publication. Three abstracts were presented at national meetings, one abstract was submitted.

CONCLUSIONS

Ketoconazole markedly suppressed serum 1,25-dihydroxyvitamin D levels in normal subjects and in patients with hyperparathyroidism or hypercalcemic sarcoidosis.

REPORT DATE: 03/14/89

WORK UNIT # 1377-86

DETAIL SUMMARY SHEET

TITLE: Quantification of Psychophysiologic Symptoms Before and After Parathyroid Surgery

KEYWORDS: hyperparathyroidism, psychology, parathyroid surgery

PRINCIPAL INVESTIGATOR: Solomon, Barbara RN DNSC

ASSOCIATES: Smallridge, Robert COL; Schaaf, Marcus MD

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Completed  
APPROVAL DATE: Apr 1986

FUNDING: Current FY: \$ 1,081 Previous FYs: \$ 0 Total: \$ 1,081

STUDY OBJECTIVE

To investigate the relationship of psychophysiologic symptoms and serum metabolic parameters between patients with primary hyperparathyroidism and benign thyroid conditions undergoing surgical therapy. To investigate any differences between the two groups of patients.

TECHNICAL APPROACH

Time series design with measurement prior to surgery and at 1, 3, and 6 months after surgery. Correlation and multivariate analysis of data are in progress.

PRIOR AND CURRENT PROGRESS

The study was completed on 1 February 1989 with 19 patients in the hyperparathyroid group and 20 patients in the thyroid control group. Collaboration with NIH on this study was terminated December 1988 due to the lack of data from NIH over a two year period. Abstract was submitted January 1989 to the Endocrine Society.

CONCLUSIONS

The HPT group had greater psychologic distress in 6 out of 9 psychologic categories and 2 of 3 global indices preoperatively. Distress improved over 6 months, but greater distress was still evident in 2 categories and 2 global indices. Although there were differences in metabolic parameters, no direct correlations were evident. It is uncertain if a metabolic parameter accounts for the difference seen and additional data analysis is being performed.

REPORT DATE: 06/28/89

WORK UNIT # 1381-86

DETAIL SUMMARY SHEET

TITLE: Effect of Obesity on Pharmacokinetics of Atropine in Young Men

KEYWORDS: obesity, atropine, pharmacokinetics

PRINCIPAL INVESTIGATOR: Smallridge, Robert COL MC

ASSOCIATES: Fein, Henry LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: Aug 1986

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine if obesity affects the pharmacokinetics of atropine sulfate.

TECHNICAL APPROACH

Atropine sulfate (2.0 mg) is given intramuscularly. Bloods are obtained frequently for 12 hours, and the serum level of atropine is measured. The pharmacokinetic parameters are determined using a computer program. Heart rate and pupil dilation are recorded as biologic responses to the drug.

PRIOR AND CURRENT PROGRESS

A total of seven (7) volunteers have been studied, and the pharmacokinetic parameters have been calculated. Due to the closure of Ward 47 for the past year, no subjects were studied during the past year. There have been no serious or unexpected side effects.

CONCLUSIONS

None

REPORT DATE: 07/28/89

WORK UNIT # 1382-86

DETAIL SUMMARY SHEET

TITLE: Long-Term Use of Somatostatin Analogue for Patients with Thyrotropin Secreting Pituitary Tumors

KEYWORDS: pituitary, somatostatin, thyrotropin

PRINCIPAL INVESTIGATOR: Smallridge, Robert COL MC

ASSOCIATES: Fein, Henry LTC MC; Ahmann, Andrew MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing

APPROVAL DATE: Aug 1986

FUNDING: Current FY: \$ 50 Previous FYs: \$ 0 Total: \$ 50

STUDY OBJECTIVE

To treat patients with thyrotropin (TSH) secreting-pituitary tumors with a somatostatin analogue (SMS 201-995) to suppress TSH secretion, if they are not cured by pituitary surgery and radiation therapy.

TECHNICAL APPROACH

Hourly blood samples for TSH levels are drawn for up to 12 hours after the initial dose and after increase in drug dose. The duration and nadir of TSH suppression will be determined. If the patient's tumor responds, he/she will be offered long-term therapy. Tumor size will be monitored with CT or MRI scans, and hormonal response with thyroid function tests.

PRIOR AND CURRENT PROGRESS

One patient remains on long-term therapy. His serum T4 and T3 levels are normal, and his TSH level is reduced, when he takes the drug at a dose of 200 mg TID. He has had no adverse reactions. His tumor size is unchanged. During the past year, this drug has become commercially available (e.g. Sandostatin) and is no longer provided by Sandoz Pharmaceuticals. The consent form has been revised accordingly.

CONCLUSIONS

This drug may be useful in the medical management of thyrotropin secreting tumors.

REPORT DATE: 08/08/89

WORK UNIT # 1383-86

DETAIL SUMMARY SHEET

TITLE: Bone Mineral Density in Subjects Treated with Thyroid Hormone

KEYWORDS: bone mineral, thyroid, osteoporosis

PRINCIPAL INVESTIGATOR: Ahmann, Andrew CPT MC

ASSOCIATES: Solomon, Barbara DNSc; Duncan, William MAJ MC

DEPARTMENT: Department of Medicine

SERVICE: Endocrine-Metabolic Service

STATUS: Completed

APPROVAL DATE: Aug 1986

FUNDING: Current FY: \$ 260 Previous FYs: \$ 1,056 Total: \$ 1,316

STUDY OBJECTIVE

To determine any negative impact of thyroid hormone on bone mineral metabolism in premenopausal women.

TECHNICAL APPROACH

Clinic charts were reviewed to find premenopausal female patients who have been on a stable dose of thyroid hormone for at least two years. They were evaluated for a variety of serum markers of calcium metabolism and bone mineral content measured by absorptiometry. The study looks at patients on thyroid hormone replacement and those on thyroid hormone suppression. It involves a cross-sectional analysis followed by longitudinal follow-up.

PRIOR AND CURRENT PROGRESS

The cross-sectional was completed in 1987 with no patients enrolled since that time. This portion of the study revealed no evidence of a correlation between bone mineral density measured in the radius, femur or spine and such variables as thyroid hormone dose, TFTs, duration of therapy and thyroid functional status. When data were reanalyzed separating patients into those without any history of higher dose and no suppression comparing results to age and weight matched patients, a slight reduction in spinal (lumbar) bone mineral density was detected in the suppressed group. Because another prospective study of thyroid hormone effect on BMD was initiated the prospective portion of this study was not continued and it has been decided to terminate this protocol.

CONCLUSIONS

Changes in BMD precipitated by thyroid hormone therapy are difficult to demonstrate in a cross-sectional study of premenopausal females. Changes found in this study of premenopausal females. Changes found in this study are minimal.

REPORT DATE: 01/03/90

WORK UNIT # 1384-86

DETAIL SUMMARY SHEET

TITLE: Calcium Supplements and Calciuria in the Elderly

KEYWORDS: calcium, calciuria, elderly

PRINCIPAL INVESTIGATOR: Duncan, William MAJ MC

ASSOCIATES: Wray, Linton COL MC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: Sep 1986

FUNDING: Current FY: \$ 4,234 Previous FYs: \$ 0 Total: \$ 4,234

STUDY OBJECTIVE

To determine if calcium carbonate given once (QD) or three times a day (TID) will cause hypercalciuria in elderly patients.

TECHNICAL APPROACH

Elderly patients will receive 900 mg of calcium carbonate (every AM or TID) or no supplement in addition to a 660 mg standardized calcium diet. Urine and serum measurements have and are still being done.

PRIOR AND CURRENT PROGRESS

Fifteen patients have completed this protocol. Analysis of the data is complete and manuscript is being finalized. Results presented as a plenary session talk at the 40th Annual Meeting of the Gerontological Society of America.

CONCLUSIONS

Calcium carbonate should be given in divided doses and that, elderly patients taking 1500 mg of elemental calcium/d, the risk of hypercalciuria is small. In addition, PTH is suppressed with TID dosing rather than once daily dosing.

REPORT DATE: 10/27/88

WORK UNIT # 1385-87

DETAIL SUMMARY SHEET

TITLE: Molecular Biology of Thyroid Disease

KEYWORDS: molecular, thyroid, biology

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC

ASSOCIATES: Baker, James MAJ MC; Wartofsky, Leonard COL MC

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Endocrine-Metabolic Service

APPROVAL DATE: Oct 1986

FUNDING: Current FY: \$20,213 Previous FYs: \$ 36,195 Total: \$ 56,408

STUDY OBJECTIVE

Clone the genes encoding for TSH receptor and TSH receptor antibody and characterize the receptor gene product.

TECHNICAL APPROACH

We are trying to clone the TSH receptor via two different methods. The first involves setting up a lambda GT11 cDNA expression library from the thyroid gland and screening expression proteins with TSH receptor antibodies, both polyclonal and monoclonal. When positive clones are found they are sequentially cloned for a minimum of five times to ensure homogeneity. At that time several studies are performed, including the growing to large numbers of inserts in plasmides and bacteria; preparation of bacterial lysates can be performed, electrophoresed, and probed using Western Blots.

PRIOR AND CURRENT PROGRESS

1) We have been successful in isolating three recombinant clones which appear to express thyroid antigens of approximately 18,000 and 65,000 molecular weight and are detected by our monoclonal antibody against the TSH receptor and not by controlled samples. We shall further characterize these inserts as indicated in the system above. 2) We have isolated these proteins by affinity chromatography utilizing TSH receptor antibody and will shortly sequence them. 3) We have determined that intrathyroidal lymphocytes from patients with autoimmune thyroid disease do not have monoclonal expression, but rather are polyclonal in nature. In contrast, lymphomas of the thyroid gland are monoclonal. 4) We have noted that in thyroïdal lymphocytes from patients with autoimmune thyroid disease have rearrangements in their DNA when probed by c-myc oncogene.

CONCLUSIONS

1) The TSH receptor is composed of 18,000 and 65,000 molecular weight antigens. 2) Intrathyroidal lymphocytes from patients with autoimmune disease show a polyclonal heterogeneity. 3) C-myc expression is unchanged in thyroid cancer and autoimmune thyroid disease. 4) EGF receptor gene may be rearranged in thyroid cancer.

REPORT DATE: 10/18/88

WORK UNIT # 1386-87

DETAIL SUMMARY SHEET

TITLE: In Vitro Determination of Messenger RNA Isolated from Porcine Thyroid Glands

KEYWORDS: messenger RNA, porcine, thyroid glands

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC

ASSOCIATES: Baker, James MAJ MC; Peele, Mark CPT MC

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Endocrine-Metabolic Service

APPROVAL DATE: Dec 1986

FUNDING: Current FY: \$ 3,979

Previous FYs: \$

0 Total: \$ 3,979

STUDY OBJECTIVE

To utilize in vitro translation of thyroid messenger RNA in order to understand the array of thyroid specific proteins that are encoded, and further, to isolate and characterize important thyroid related proteins such as the TSH receptor.

TECHNICAL APPROACH

Isolation of messenger RNA from pork thyroid glands is performed by standard GTC extraction techniques. The messenger RNA is obtained by poly A+ RNA chromatography, and the messenger RNA obtained is translated with an S labelled into specific proteins. These specific proteins are then electrophoresed on one or two dimensional gels with the proteins obtained then identified. Both pork thyroid glands and hepatic samples are used. Also, specific antibodies can be utilized against the proteins to determine which proteins are of interest, such as to recognize the TSH receptor.

PRIOR AND CURRENT PROGRESS

We have performed approximately 10-15 translations and have identified specific proteins that are present in thyroid and not liver. We are in the process of identifying these proteins.

CONCLUSIONS

There are thyroid specific proteins that have various molecular weights present within the thyroid glands and specific efforts to identify the molecular weights of these proteins and their physical chemical determination are proceeding.

REPORT DATE: 09/03/88

WORK UNIT # 1387-87

DETAIL SUMMARY SHEET

TITLE: Dissolution of Commercial Oral Calcium Carbonate Supplements

KEYWORDS: dissolution, calcium

PRINCIPAL INVESTIGATOR: Duncan, William MAJ MC

ASSOCIATES: Wray, Linton COL MC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: Jan 1987

FUNDING: Current FY: \$11,833 Previous FYs: \$ 13,021 Total: \$ 24,854

STUDY OBJECTIVE

To determine the in vitro dissolution of commercially available oral calcium carbonate supplements.

TECHNICAL APPROACH

Dissolution is being tested by method II of the U.S. Pharmacopoeia.

PRIOR AND CURRENT PROGRESS

Twenty seven calcium carbonate preparations have been tested and only 5 have met USP Standards. In vitro dissolution correlates with the filler content of each tablet but not the stated calcium content, chemical sources of the calcium, retail cost pill hardness or retail source. A manuscript is in preparation.

CONCLUSIONS

These results raise concern about the bioavailability of the calcium in these preparations.

REPORT DATE: 07/10/89

WORK UNIT # 1389-87

DETAIL SUMMARY SHEET

TITLE: 1,25-Dihydroxyvitamin D3 Induction of Ornithine Decarboxylase Activity in Regenerating Rat Liver

KEYWORDS: 1,25-Dihydroxyvitamin, ornithine decarboxylase, liver

PRINCIPAL INVESTIGATOR: Duncan, William MAJ MC  
ASSOCIATES: Wray, Linton COL MC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: May 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine whether 1,25(OH)2D3 induces ornithine decarboxylase (ODC) activity via a receptor (genomic) mechanism in regenerating rat liver.

TECHNICAL APPROACH

ODC activity and oncogene expression is measured in regenerating liver from vitamin D deficient and vitamin D treated rats.

PRIOR AND CURRENT PROGRESS

The hepatic nuclear 1,25(OH)2D3 receptor has been demonstrated by us to rapidly decrease in regenerating rat liver. A detailed analysis of the time course shows that the receptor decreased 64% 2 hours after hepatectomy and slowly returned to pre-hepatectomy values by 32 hours. On the other hand, ODC activity is maximal at 16 hours and c-myc proto-oncogene mRNA expression is maximal at 2 hours after hepatectomy.

CONCLUSIONS

The rise in c-myc and ODC expression during liver regeneration is associated with a fall, not a rise, in expression of the vitamin D receptor. Thus, these activities may not be linked to receptor mediated 1,25(OH)2D3 action in the regenerating liver.

REPORT DATE: 03/15/89

WORK UNIT # 1390-87

DETAIL SUMMARY SHEET

TITLE: Dynamic Assessment of Zinc Status in Thyroid Disease

KEYWORDS: zinc, hyperthyroidism, hypothyroidism

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC

ASSOCIATES: Wartofsky, Leonard COL MC; Solomon, Barbara DNSC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: May 1987

FUNDING: Current FY: \$ 2,650 Previous FYs: \$ 0 Total: \$ 2,650

STUDY OBJECTIVE

To investigate zinc homeostasis in thyroid disease.

TECHNICAL APPROACH

There have been no side effects during the four-hour zinc tolerance test. Nutrient data have been collected but not analyzed as yet. No protocol modifications are proposed.

PRIOR AND CURRENT PROGRESS

Sixteen (16) hypothyroid, five (5) hyperthyroid and eight (8) normal volunteers have completed the study. All blood and urine samples have been analyzed. Nutritional data are being analyzed. Data are in the process of being entered into the computer for statistical analysis. It is unknown at this time whether the study can be completed or whether additional hyperthyroid subjects will be required.

CONCLUSIONS

No conclusion can be drawn at this time.

REPORT DATE: 07/10/89

WORK UNIT # 1391-87

DETAIL SUMMARY SHEET

TITLE: Bone Mineral Density (BMD) in Patients with Chronic Renal Failure

KEYWORDS: bone mineral, renal failure

PRINCIPAL INVESTIGATOR: Duncan, William LTC MC

ASSOCIATES: Gouge, Steven MAJ MC; Moore, Jack LTC MC

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Endocrine-Metabolic Service

APPROVAL DATE: Jun 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To correlate bone mineral density measurements at the spine and forearm with clinical and laboratory parameters of patients with chronic renal failure.

TECHNICAL APPROACH

This is a pilot retrospective chart review of patients with chronic renal failure who have had forearm and spine bone mineral density measurements.

PRIOR AND CURRENT PROGRESS

Data collection is completed and analyzed. Results indicate that in chronic renal failure, bone loss is primarily cortical and that measurement of trabecular bone adds little to the evaluation of patients with chronic renal failure. Eighty-one charts were reviewed.

CONCLUSIONS

Forearm densitometry is the test of choice to follow the status of bone in patients with chronic renal failure.

REPORT DATE: 07/17/89

WORK UNIT # 1392-87

DETAIL SUMMARY SHEET

TITLE: Role of 1,25(OH)2D3 in Liver Regeneration

KEYWORDS: 1,25 (OH)2D3, liver, regeneration

PRINCIPAL INVESTIGATOR: Duncan, William LTC MC

ASSOCIATES: Wray, Linton COL MC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: Jul 1987

FUNDING: Current FY: \$ 371 Previous FYs: \$ 0 Total: \$ 371

STUDY OBJECTIVE

To determine the effects of 1,25(OH)2D3 on hepatocyte proliferation.

TECHNICAL APPROACH

The regenerating rat liver will be used as the model for proliferating hepatocytes. Liver weight, DNA synthesis, ornithine decarboxylase activity, adenylate cyclase activity, c-myc expression and 1,25(OH)2D3 receptor concentration will be measured after partial hepatectomy in vitamin D treated rats.

PRIOR AND CURRENT PROGRESS

This proposal was not funded by the VA-DOD collaborative study. Pending further experimental results, this proposal may be resubmitted.

CONCLUSIONS

None.

REPORT DATE: 07/10/89

WORK UNIT # 1393-87

DETAIL SUMMARY SHEET

TITLE: Regulation of Rat TSH Beta Subunit Gene Expression

KEYWORDS: TSH, gene, rodent

PRINCIPAL INVESTIGATOR: Carr, Frances PhD

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: Aug 1987

FUNDING: Current FY: \$26,610 Previous FYs: \$ 77,234 Total: \$ 103,844

STUDY OBJECTIVE

The objective is to determine how the structure of the B-subunit gene of rat thyrotropin defines the functional response of the gene (including hormonal regulation) by thyroid hormones and tissue-specific expression.

TECHNICAL APPROACH

Chimaeric plasmids encompassing various portions of the 5'-end of the rat TSH B-subunit gene are constructed by fusion of the eukaryotic gene sequence with the coding sequence of a reporter enzyme (specifically bacterial chloramphenicol acetyl transferase-CAT). Transient expression in eukaryotic cells is then used to identify the cis elements responsible for hormonal regulation in a responsive cell line and those responsible for cell-specific expression in non-responsive cell lines. Then, DNA-protein interaction assay (DNase I protection and gel shift assays) are used to identify DNA binding proteins that affect transcription, such as the thyroid hormone receptor.

PRIOR AND CURRENT PROGRESS

We have localized the DNA sequence required for thyroid hormone regulation of TSHB subunit gene expression. Moreover we have by deletion analyses focused on 180 bases of 5' flanking sequence as critical for TRH stimulation of TSH gene expression. The possible mechanism(s) of TRH stimulation of gene expression are currently being explored to understand the intracellular signaling mechanisms of TRH. We have recently established that intracellular calcium flux and protein kinase C are key factors. Possible activation via oncogenes c-jun and c-fos are currently being explored.

CONCLUSIONS

1. TSH regulates TSHB and subunits through unique DNA sequences that block transcription activation. 2. TRH expression via intracellular calcium and protein kinase C.

REPORT DATE: 06/27/89

WORK UNIT # 1394-87

DETAIL SUMMARY SHEET

TITLE: Molecular Biology of Nutrient Alterations in Rats

KEYWORDS: molecular biology, nutrition, glucose

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC  
ASSOCIATES: Carr, Frances PhD; Glass, Alan COL MC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: Aug 1987

FUNDING: Current FY: \$ 9,174 Previous FYs: \$ 11,696 Total: \$ 20,870

STUDY OBJECTIVE

We shall: a) examine changes in expression of the insulin receptor (IR) gene and glucose transporter (GT) gene in rats ingesting various dietary regimens known to alter insulin binding, such as caloric restriction, sucrose and fat overfeeding, and copper deficiency; b) identify mRNA hybridization to IR and GT cDNA probes in rat tissues, including adipocytes and hepatocytes; and c) document changes in proto-oncogene expression induced by these dietary maneuvers.

TECHNICAL APPROACH

Rats are divided into eight dietary groups so that the effect of nutritional alterations can be studied in various aspects of DNA and RNA. The diet groups include a control, total calorie restricted, high fat, pair fed, high sucrose, and copper deficient groups. After eating this diet for about three months, the rats are sacrificed and liver and fat RNA and DNA are isolated from each organ. These samples are then electrophoresed and transferred to membranes; they are then probed by various labeled nucleotide probes to include: glucose transporter, insulin receptor, erb A, and other oncogenes.

PRIOR AND CURRENT PROGRESS

All of the actual animal studies have been accomplished and many of the samples of nucleotides with several probes show that the techniques were fine. Now we shall start to use the probes of interest. The insulin receptor probe was given to us by Dr. Graeme Bell, the glucose transporter by Dr. Mueckler and the erb A by Drs. Usala and Weinberger. We have worked diligently over the last year to define optimal conditions for hybridization studies and we hope to have results this coming year.

CONCLUSIONS

None yet.

REPORT DATE: 08/16/89

WORK UNIT # 1395-87

DETAIL SUMMARY SHEET

TITLE: Oncogenes and Thyroid Receptors

KEYWORDS: oncogenes, thyroid

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC

ASSOCIATES: Carr, Frances PhD; Teriansky, George CPT MC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: Sep 1987

FUNDING: Current FY: \$44,478      Previous FYs: \$ 13,877      Total: \$ 58,355

STUDY OBJECTIVE

The purpose of this protocol is to determine whether oncogenes are expressed viably in thyroid tissue derived from patients with different thyroid diseases. Further, patterns of DNA hybridization will help determine if amplified or rearranged genes exist.

TECHNICAL APPROACH

DNA and/or RNA are extracted by standard guanidinium gradients. The nucleotides obtained are then subjected to gel electrophoresis and then transferred to nylon or nitrocellulose. These membranes are then probed and high specific activity P32 labelled inserts or plasmids. Results are quantitated visually and by spectrophotometer readings, after autoradiography and development. Abnormal pattern of hybridization may indicate expression abnormalities in RNA or amplification or rearrangement abnormalities in DNA.

PRIOR AND CURRENT PROGRESS

We have been very successful in developing and refining techniques to isolate, purify, electrophorese, transfer, and hybridize RNA and DNA. We have obtained samples from patients with thyroid cancer, nodules, and goiter. Using cERB B gene probe we have noted that several cell lines have rearranged genes, but none of the thyroid tissue analyzed show a consistent abnormality. We plan to continue to study the thyroid cell lines that demonstrate gene rearrangements and also will now proceed to examine hybridization patterns to other oncogenes, such as ERB A, NEU, MYB. Further, we will use other probes as they are developed, such as the TSH receptor probe or ANF probe, to help understand the abnormalities in thyroid tissue. Viral probes will also be used.

CONCLUSIONS

Thyroid cell lines may grow by virtue of the fact they have rearranged genes for growth factors, but other oncogenes, such as c-myc and c-ERB B probably do not play an integral role in determining how thyrocytes grow and divide.

REPORT DATE: 01/17/89

WORK UNIT # 1396-87

DETAIL SUMMARY SHEET

TITLE: The Effect of Exogenously Administered Levothyroxine on Bone Mineral Content (BMC)

KEYWORDS: thyroxine, bone

PRINCIPAL INVESTIGATOR: Burch, Henry CPT MC

ASSOCIATES: Duncan, William LTC MC; Ahmann, Andrew MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: Sep 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine the effects of short and intermediate term thyroxine therapy on bone calcium content when given to humans for replacement of a hormone deficiency or for suppression of thyrotropin. Studies in this area have been inconsistent.

TECHNICAL APPROACH

We are hoping to detect significant changes in bone mineral density (BMD) by following patients closely in a prospective manner from the time of hormone therapy initiation. Women are recruited for enrollment in the study at the time of diagnosis of hypothyroidism or a probable benign thyroid abnormality requiring thyroxine for suppression. Serum is analyzed for thyroid function test, calcium, alkaline phosphatase, and osteocalcin at 0, 3, 6 and 12 months. BMD is performed by photon absorptiometry at the same intervals. The results will be analyzed using multiple regression with the primary dependent variable being the slope of change of BMD.

PRIOR AND CURRENT PROGRESS

The protocol was approved by the HUC/IRB in September 1987 and final approval was transmitted from DCI on 23 October 1987. Since then, eight patients have enrolled in the study. One patient dropped out of the study after the initial evaluation due to inconvenience. Five patients now have multiple time points in data collection. Four of these five patients are in the hypothyroid group. No apparent changes in BMD have been observed although statistical analysis is not possible on so few patients. No new literature has been published to alter our initial impressions or perceived need for the study. No complications have resulted from the protocol, and patients have been quite cooperative.

CONCLUSIONS

Insufficient data base to render conclusions from our study. The literature has not clarified the question of bone consequences of typical thyroxine hormone doses. A control group would add significant credibility to our results given the recent discussion of this problem at national meetings.

REPORT DATE: 10/10/89

WORK UNIT # 1397-87

DETAIL SUMMARY SHEET

TITLE: Intestinal Absorption of Commercial (Oral) Calcium Carbonate Supplements

KEYWORDS:

PRINCIPAL INVESTIGATOR: Brennan, Michael LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Completed  
APPROVAL DATE: Oct 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine if calcium supplements with excellent dissolution characteristics in vitro have different absorption in vivo than calcium supplements with fair or poor dissolution characteristics.

TECHNICAL APPROACH

Six volunteers underwent a 13 day protocol which included low calcium diets and calcium loading with calcium carbonate preparations with excellent, fair and poor in vitro dissolution characteristics. Calcium absorption was evaluated using fractionated urine calcium measurements.

PRIOR AND CURRENT PROGRESS

Six volunteers were enrolled under the study protocol. We did not see any definite significant differences in calcium absorption across the 3 groups of calcium carbonate pills. There were major technical difficulties in obtaining reliable, reproducible measurements of urine calcium. Based on the large amount of volunteer and investigator time and effort required, and after on the negative results, the study was terminated.

CONCLUSIONS

There were no significant differences in calcium absorption across the 3 groups of calcium carbonate supplements. The lack of difference may have been due to technical difficulties involved in calcium measurement, difficulties which we were unable to resolve. This study was terminated.

REPORT DATE: 10/13/88

WORK UNIT # 1398-87

DETAIL SUMMARY SHEET

TITLE: The Management of Hyperthyroidism Due to Graves' Disease in the United States

KEYWORDS: management, Graves' disease

PRINCIPAL INVESTIGATOR: Solomon, Barbara DNSc

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Completed  
APPROVAL DATE: Nov 1987

FUNDING: Current FY: \$ 101 Previous FYs: \$ 0 Total: \$ 101

STUDY OBJECTIVE

a) Determine which tests are available for diagnosis of Graves' Disease and are currently being used; b) Determine trends for the management of Graves' disease; c) Determine trends for how the therapeutic options are being implemented. 4) Compare U.S. trends to those previously reported for the ETA.

TECHNICAL APPROACH

Survey by questionnaire SPSS Program using Fortran language with outcome of percentages by category and contingency tables for basic analysis. SPSS program for Chi Square of comparative data.

PRIOR AND CURRENT PROGRESS

Survey completed: February 1988. Basic data analysis completed: March 1988. Comparative data analysis completed: May 1988. Abstract submitted: June 1988. Abstract presented: September 1988.

CONCLUSIONS

Test for dx include T4, T3, FTI, TSH and uptake only. RI chosen for index pt and 7/8 variations. Differences from ETA in tests used and treatment of pts. When ATD use PTU, preferred over MMI.

REPORT DATE: 11/01/88

WORK UNIT # 1399-87

DETAIL SUMMARY SHEET

TITLE: Growth Factors and the Thyroid Gland

KEYWORDS: human thyroid, EGF, ANP

PRINCIPAL INVESTIGATOR: Tseng, Yueh-Chu PhD

ASSOCIATES: Wartofsky, Leonard COL MC; Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine  
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing  
APPROVAL DATE: Dec 1987

FUNDING: Current FY: \$24,061 Previous FYs: \$ 0 Total: \$ 24,061

STUDY OBJECTIVE

To determine the role of epidermal growth factor (EGF), atrial natriuretic peptide (ANP) and their respective receptors in the maintenance of cultured human thyroid cells derived from surgery removed thyroids with various diseased states.

TECHNICAL APPROACH

a) Primary thyroid cell culture was established by digesting human thyroid tissues with collagenase, collecting the thyroid cells, then growing cells in proper plates for experiments; b) EGF and ANP receptors on thyroid cells were assayed by Scatchard analysis to determine the number of receptor binding sites and their respective binding association constraints; c) Effects of EGF and ANP on thyroglobulin (Tg) secretion by thyroid cells was determined by assaying Tg concentration media using ELISA.

PRIOR AND CURRENT PROGRESS

More than 40 human thyroid tissues were processed, with approximately 18 yielding enough cells to do the experiments. Cultured thyroid cells were used to study the effect of the above hormones on thyroglobulin release, thymidine incorporation into DNA, and cyclic AMP production. Our use of part of surgically removed thyroid tissues did not interfere with patients' well-being. Patients are not directly benefiting from the the results of this study.

CONCLUSIONS

EGF and ANP receptor were found on human thyroid cells, and the number of receptor binding sites were modulated by TSH. EGF and ANP also affect Tg secretion by cultured thyroid cells. Two manuscripts were submitted with reviewer's comments requiring larger sample size. Continued collection of data on more thyroid tissues is needed to warrant final publication.

REPORT DATE: 12/08/89

WORK UNIT # 1400-88

DETAIL SUMMARY SHEET

TITLE: A Pilot Study Evaluating Intestinal and Serum Immunoglobulin Levels in Patients with Acquired Hypogammaglobulinemia and Recurrent/Chronic Diarrhea of Undefined Etiology

KEYWORDS: immunoglobulins, hypogammaglobulinemia, diarrhea

PRINCIPAL INVESTIGATOR: Decker, Robert CPT MC

ASSOCIATES: Shea, Steve COL MC; Engler, Reneta LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Ongoing  
APPROVAL DATE: Feb 1988

FUNDING: Current FY: \$ 2,658 Previous FYs: \$ 0 Total: \$ 2,658

STUDY OBJECTIVE

a) To develop an IgG-subclass specific ELISA for measurement of G1/G2/G3 and G4 levels in intestinal secretions; b) To measure quantitative immunoglobulin levels, particularly IgG subclasses, in the intestinal secretions of patients with common variable hypogammaglobulinemia and compare these with normal levels.

TECHNICAL APPROACH

Secretions previously collected under protocol #1453 (normals) and those stored from medically indicated evaluations (hypogammaglobulinemic patients with diarrhea) will be utilized for study. An ELISA utilizing highly specific monoclonal antibodies to human G subclasses will be developed. Results are to be standardized to a uniform reference and quantitated.

PRIOR AND CURRENT PROGRESS

Initial baseline experiments were performed but were complicated by low level detection requirements and excessive background activity from secretions versus serum. Transfer of principal and collaborative investigators also hampered continued progress of the project.

CONCLUSIONS

Technical difficulties in the G subclass ELISA may be overcome by the availability of purified subclass reagents (previously only in ascites). Additional technical support in the laboratory spaces should facilitate work on this project in the future.

REPORT DATE: 09/13/89

WORK UNIT # 1401

DETAIL SUMMARY SHEET

TITLE: The Effect of Normalization of Intraesophageal pH on Mucosal Proliferation in Barrett's Esophagus

KEYWORDS: Barrett's esophagus, gastroesophageal reflux, proliferation

PRINCIPAL INVESTIGATOR: Phillips, Raymond MAJ MC

ASSOCIATES: Maydonovitch, Corinne BS; Wong, Roy COL MC

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Ongoing

APPROVAL DATE: Sep 1988

FUNDING: Current FY: \$ 226 Previous FYs: \$ 0 Total: \$ 226

STUDY OBJECTIVE

Barrett's esophagus (BE) is a columnar epithelium with premalignant potential which develops in response to prolonged and severe gastroesophageal reflux (GER). The study objective is to normalize the intraesophageal pH with a potent H<sub>2</sub> antagonist (famotidine) and then observe the effect on mucosal proliferation as assessed by ornithine decarboxylase activity and thymidine uptake.

TECHNICAL APPROACH

Patients (10) with BE who have reflux by 24 hour ambulatory esophageal pH study (EPS) will undergo first EGD to obtain biopsies of BE to measure mucosal proliferation rate. Famotidine 40 mg PO BID will be started; an EPS will be repeated after 1 week. If the esophageal pH is still < 4 the dosage of famotidine for 30 days when a second EGD with biopsies and an EPS will be completed. After 30 more days of famotidine a third EGD with biopsies and a final EPS will be completed.

PRIOR AND CURRENT PROGRESS

The equipment and supplies necessary to initiate the project have been assembled. A tabulation of patients with Barrett's esophagus at Walter Reed Army Medical Center has been completed. One patient has been enrolled.

CONCLUSIONS

None at this time.

REPORT DATE: 09/28/89

WORK UNIT # 1432

DETAIL SUMMARY SHEET

TITLE: Lithium, Nicotinic Acid, Aminophylline, and 16,16 Dimethyl PGE2 as Cytoprotective Agents

KEYWORDS: cytoprotection, lithium, gastric emptying

PRINCIPAL INVESTIGATOR: Wong, Roy COL MC

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Ongoing  
APPROVAL DATE: Sep 1980

FUNDING: Current FY: \$ 1,678 Previous FYs: \$ 185 Total: \$ 1,863

STUDY OBJECTIVE

To determine the cytoprotective properties of lithium on the gastric mucosa in rats and to compare it to other similar agents. To relate the cytoprotective effect of these agents to gastric emptying and to determine the mechanism of action.

TECHNICAL APPROACH

Cytoprotection studies are performed utilizing an ethanol-induced hemorrhagic gastric study model where control and treatment animals are gavage fed 1cc 95% ethanol and then sacrificed one hour later for removal of stomach and grading of gastritis. Gastric emptying studies are performed by gavage feeding control and treatment animals 1cc Cr51-labelled water, and then 30 min later sacrificing the animal to remove stomach and count residual Cr51.

PRIOR AND CURRENT PROGRESS

We have performed cytoprotection studies in several different groups of rats treated with lithium and/or 4 prokinetic drugs, cisapride, domperidone, urecholine and metochlopramide in order to assess lithium's cytoprotective properties against ethanol induced hemorrhagic gastritis. In effort to block this effect, we combined the treatment of lithium with prokinetic agents.

CONCLUSIONS

Lithium is a potent gastric cytoprotective agent which significantly decreases acid secretion and increases gastric emptying. Lithium's effect is significantly blocked by metochlorpromid. Data are being collected for a manuscript.

REPORT DATE: 10/20/88

WORK UNIT # 1435

DETAIL SUMMARY SHEET

TITLE: Genetic Linkage in Achalasia

KEYWORDS: achalasia, HLA typing, genetic linkage

PRINCIPAL INVESTIGATOR: Wong, Roy COL MC

ASSOCIATES: Maydonovitch, Corinne

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Ongoing

APPROVAL DATE: Dec 1980

FUNDING: Current FY: \$ 239 Previous FYs: \$ 75 Total: \$ 314

STUDY OBJECTIVE

To determine if there is a genetically related association in achalasia.

TECHNICAL APPROACH

Perform HLA typing on patients seen in the gastroenterology clinic with documented achalasia or other motor disorders of the esophagus.

PRIOR AND CURRENT PROGRESS

We have studied 40 patients with documented achalasia. We would like to study more patients with other motor disorders and also increase the number of black patients with achalasia.

CONCLUSIONS

The results show a positive association for the class II HLA antigen DQw1 in caucasian achalasia patients ( $P < 0.02$ ) and Black patients (NS).

REPORT DATE: 04/04/89

WORK UNIT # 1448

DETAIL SUMMARY SHEET

TITLE: Effects of Semi-Chronic Ingestion of Lithium and Acetylsalicylic Acid on Rat Gastric Mucosa and Kidney

KEYWORDS: lithium, acetylsalicylic acid, gastric mucosa

PRINCIPAL INVESTIGATOR: Wong, Roy COL MC  
ASSOCIATES: Maydonovitch, Corinne

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Ongoing  
APPROVAL DATE: May 1982

FUNDING: Current FY: \$ 153 Previous FYs: \$ 6,055 Total: \$ 6,208

STUDY OBJECTIVE

To determine the semi-chronic cytoprotective effects of lithium on aspirin-induced GI ulceration along with possible nephrotoxicity of the combination of lithium and aspirin.

TECHNICAL APPROACH

Animals will be given aspirin PO and lithium chloride subcutaneously for a period of 7, 14, 21, and 28 days. Chromium labelled RBC's will then be administered 24 hours prior to sacrifice and stools collected to measure gastrointestinal blood loss. At the time of sacrifice, stomach and renal tissue will be removed to determine any changes and eventually histologically reviewed to determine any changes related either to lithium or aspirin.

PRIOR AND CURRENT PROGRESS

Utilizing a chronic model for GI ulceration, rats were pretreated with lithium chloride, 30mg/kg p.o. or water one hour prior to administration of 2cc acetylsalicylic acid solution twice daily (200mg/kg p.o.). Our data have shown that lithium choloride pretreatment is cytoprotective in this model. To further investigate our results and possible mechanisms, we would like to study blood flow and gastric emptying in this model.

CONCLUSIONS

Conclusions from current data are that rats pretreated with lithium chloride had lower GI ulceration scores than those pretreated with water. Possible mechanisms for this need to be investigated.

REPORT DATE: 01/12/90

WORK UNIT # 1449

DETAIL SUMMARY SHEET

TITLE: How Has Cimetidine Affected the Treatment of Peptic Ulcer Disease

KEYWORDS: drug therapy, cimetidine, peptic ulcer therapy

PRINCIPAL INVESTIGATOR: Gage, Thomas COL MC

DEPARTMENT: Department of Medicine

STATUS: Terminated

SERVICE: Gastroenterology Service

APPROVAL DATE: May 1982

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

1. To assess the proportion of radiologically-diagnosed peptic ulcer patients treated with histamine-2 (H-2) blockers. 2. To determine by patient interview and chart review how these drugs are prescribed (dosage & duration).

TECHNICAL APPROACH

1. Prospective study patients are identified in Radiology when an acute gastric or duodenal ulceration is noted. 2. Patients are contacted by the principal investigator approximately six months later and are queried regarding their method of treatment. Interviews are conducted by telephone or in person.

PRIOR AND CURRENT PROGRESS

Twenty-seven patients have been enrolled thus far. Twenty-one of the twenty-seven patients have been treated with H-2 blockers. Of the twenty-seven patients or approximately 40%, were treated with both antacids and cimetidine, neither on an "as needed" basis. This may constitute systematic over-treatment.

CONCLUSIONS

ADMINISTRATIVELY TERMINATED

REPORT DATE: 05/16/89

WORK UNIT # 1450

DETAIL SUMMARY SHEET

TITLE: Adenomatous Colonic Polyps: A Vitamers and MFO Induction

KEYWORDS: colon polyps, vitamin A, beta carotene

PRINCIPAL INVESTIGATOR: Kikendall, James LTC MC

ASSOCIATES: Burgess, Mary RD; Bowen, Phyllis RD PhD

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Ongoing  
APPROVAL DATE: Jul 1982

FUNDING: Current FY: \$ 734 Previous FYs: \$ 12,016 Total: \$ 12,750

STUDY OBJECTIVE

a) Case control portion: To evaluate risk factors for colonic adenomas. b)  
Intervention portion: to evaluate beta carotene, 15mg PO daily, as a colon  
cancer chemopreventive agent.

TECHNICAL APPROACH

a) Case control portion: Subjects who report for indicated colonoscopy who meet entry criteria are assessed by dietary and historical interview and sampling of blood and urine. Subjects with polyps (adenomas) and colonoscopy - negative controls are compared. b) Intervention Study: Subjects are randomized to received placebo or beta carotene after removal of colonic adenomas. Repeat colonoscopy assesses recurrence over the subsequent three years. Although beta carotene is not known to have any harmful side effects, several potential side effects are monitored.

PRIOR AND CURRENT PROGRESS

a) Case control portion: Data were collected for 361 subjects. Only smoking and alcohol consumption data have been analyzed sufficiently to permit publication. Analysis of other data requires additional major funding for computer input, etc. We recently applied for a \$50,000 grant from the American Institute for Cancer Research (submitted under separate cover). b) Intervention Study: 275 subjects were randomized. One hundred sixty have completed the 3 year intervention. The last subjects will complete the trial in June 1990.

CONCLUSIONS

Smoking and alcohol are independent risk factors for colonic adenomas. Very incomplete analysis suggests that low dietary carotenoids are associated with adenomas and that low serum selenium is associated with early colon cancer. Smoking is associated with low serum beta carotene.

REPORT DATE: 10/26/89

WORK UNIT # 1453

DETAIL SUMMARY SHEET

TITLE: The Effect of Sodium Deprivation on Small Intestinal Water and Electrolyte Transport

KEYWORDS: intestinal transport, sodium depletion

PRINCIPAL INVESTIGATOR: Decker, Robert MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Ongoing  
APPROVAL DATE: Oct 1983

FUNDING: Current FY: \$ 49 Previous FYs: \$ 0 Total: \$ 49

STUDY OBJECTIVE

To resolve the following questions: 1) What are the water and electrolyte transport rates in jejunum and ileum as determined by triple lumen perfusion in normal volunteers at WRAMC? 2) What effect does salt restriction have on intestinal absorptive ability, determined by triple lumen tube intestinal perfusion?

TECHNICAL APPROACH

Volunteers are initially studied over a two-day period as inpatients during which time triple-lumen tube is passed orally into the small intestine and positioned by fluoroscopy. Subsequently a standard Ringer's-like solution, a glucose-sodium chloride solution, and a mannitol-sodium chloride solution are infused for a period of approximately 4 hours during each of the two days.

PRIOR AND CURRENT PROGRESS

No new patients have been enrolled since the last report. A manuscript describing conclusion #1 below has been submitted to a peer review journal and rejected. A second manuscript detailing conclusion #2 below is in preparation. A delay in preparation of the manuscript is due to the principal investigator, COL Gage, having left the military. A new principal investigator, MAJ Decker and a new associate investigator, COL Wong, have been appointed to complete the project.

CONCLUSIONS

1) Short term (72 hr) sodium depletion has no appreciable effect on sodium and water transport in the ileum. 2) Intestinal IgA secretion is significantly greater in the jejunum than the ileum and does not correlate with water transport.

REPORT DATE: 07/10/89

WORK UNIT # 1462

DETAIL SUMMARY SHEET

TITLE: The Evaluation of Postprandial Supine Reflux Events by Simultaneous Esophageal Manometry, Esophageal pH Monitoring, and Gastroesophageal Scintiscanning in Patients with Hiatus Hernia and Esophagitis

KEYWORDS: reflux, manometry, scintigraphy

PRINCIPAL INVESTIGATOR: Shay, Steven COL MC

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Ongoing  
APPROVAL DATE: Aug 1983

FUNDING: Current FY: \$ 1,800 Previous FYs: \$ 1,121 Total: \$ 2,921

STUDY OBJECTIVE

To correlate the presence, approximate volume, and clearance of gastroesophageal reflux by scintiscan with reflux events and clearance as determined by pH changes. To evaluate temporal relationships of hiatal hernia filling and emptying as determined by scintiscan with gastroesophageal reflux determined by scintiscan and pH changes.

TECHNICAL APPROACH

Patients with symptoms of gastroesophageal reflux and severe endoscopic esophagitis are included. An esophageal pH probe and manometry catheter are passed per nares to measure simultaneous manometry and pH monitoring. The patients ingest a study meal consisting of commercial beef stew, 15 lamb liver cubes, and 250 cc of water, each labeled with 50 uCu of 99m Technesium sulfur-colloid. The patients lay on the left and right side alternately for a total of 4-10 minute recumbent monitoring periods.

PRIOR AND CURRENT PROGRESS

A total of ten patients and five volunteers have been entered into the study. Thus, no additional patients have been added since last progress report. The ideal patient is hard to find, and of all the GI protocols, this one has a low priority. However, we do plan to enter more patients and request that status be ongoing.

CONCLUSIONS

Pending.

REPORT DATE: 01/12/90

WORK UNIT # 1464

DETAIL SUMMARY SHEET

TITLE: The Effect of Paracentesis on Pulmonary Function in Cirrhotics with Ascites and Dyspnea

KEYWORDS: paracentesis, ascites, dyspnea

PRINCIPAL INVESTIGATOR: Gage, Thomas

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Terminated  
APPROVAL DATE: Feb 1984

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine what effect a large volume paracentesis has on pulmonary function in cirrhotics.

TECHNICAL APPROACH

Lung volumes, flow rates, transdiaphragmatic pressure, and arterial blood gases are obtained before and after a large volume paracentesis.

PRIOR AND CURRENT PROGRESS

During previous fiscal year two patients were enrolled; during the current fiscal year, five patients were considered eligible; however, four were not studied as they either refused to participate or were not able to be scheduled in the pulmonary function laboratory.

CONCLUSIONS

ADMINISTRATIVELY TERMINATED

REPORT DATE: 04/24/89

WORK UNIT # 1466

DETAIL SUMMARY SHEET

TITLE: Validation and Reliability Rating of a Vitamin A Diet History

KEYWORDS: diet history, vitamin A

PRINCIPAL INVESTIGATOR: Kikendall, James LTC MC

ASSOCIATES: Burgess, Mary MS RD

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Completed  
APPROVAL DATE: Jun 1984

FUNDING: Current FY: \$ 218 Previous FYs: \$ 95 Total: \$ 313

STUDY OBJECTIVE

To assess the validity and reliability of a dietary questionnaire that is used in protocol 1450.

TECHNICAL APPROACH

The dietary questionnaire is administered to an individual twice. The reproducibility is determined by comparing the responses obtained at the two intervals. The validity is determined from a comparison with records and serum levels.

PRIOR AND CURRENT PROGRESS

Collection of data for this project has been completed. Analysis has not been performed due to reduction of personnel and other priorities for available personnel. If protocol 1450 is refunded, these data will be analyzed to the extent necessary to support that project.

CONCLUSIONS

Pending analysis.

REPORT DATE: 10/27/89

WORK UNIT # 1470

DETAIL SUMMARY SHEET

TITLE: Intestinal Sodium and Water Transport: Evaluating Solutions to Maximize Absorption

KEYWORDS: short bowel syndrome, intestinal absorption, intestinal transport

PRINCIPAL INVESTIGATOR: Decker, Robert MAJ MC

ASSOCIATES: Wong, Roy COL MC

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Ongoing  
APPROVAL DATE: Aug 1984

FUNDING: Current FY: \$ 623 Previous FYs: \$ 944 Total: \$ 1,567

STUDY OBJECTIVE

The study objective is to evaluate oral rehydration formulas (ORF's) containing different carbohydrate moieties to determine an optimal solution for treatment of short bowel syndrome and acute diarrheal illnesses. (Unchanged from initial application)

TECHNICAL APPROACH

The first part of the study utilizes the triple-lumen intestinal perfusion technique in normal volunteers to assess the relative contribution of active vs passive carbohydrate absorption in promoting salt and water absorption; in the second part, ORF's are infused in patients with short bowel syndrome measurements of ostomy output used to assess efficacy. There have been two minor protocol modifications, the first relates to solution infusion rate in part B this has been increased to 150ml/hr from 100ml/hr. The 2nd modification deleted codeine IM and substitutes paregoric 10 cc's orally as the antiperistaltic agent.

PRIOR AND CURRENT PROGRESS

No additional patients have been recruited during the recent fiscal year due to the Principal Investigator, COL Thomas Gage, having left the military. Four patients constitute the study group at present. A new Principal Investigator, MAJ Robert Decker, and a new Associate Investigator, COL Roy Wong, have been appointed to resume and complete the project.

CONCLUSIONS

Conclusions are unchanged from the detail summary of 1987. It appears that the WHO oral rehydration formula is more efficient than a Polycose-electrolyte solution.

REPORT DATE: 10/18/89

WORK UNIT # 1471

DETAIL SUMMARY SHEET

TITLE: Serum and Tissue Zinc Levels in the Esophagus

KEYWORDS: zinc, esophagus

PRINCIPAL INVESTIGATOR: Wong, Roy COL MC

ASSOCIATES: Maydonovitch, Corinne MS

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Ongoing  
APPROVAL DATE: Aug 1984

FUNDING: Current FY: \$ 521 Previous FYs: \$ 1,028 Total: \$ 1,549

STUDY OBJECTIVE

To determine zinc levels in serum, gastric fluid, and esophageal tissue of patients with Upper Gastrointestinal diseases such as squamous cell carcinoma, reflux esophagitis, duodenal and gastric ulcer disease and in normals.

TECHNICAL APPROACH

At the time of endoscopy, 15cc of blood and biopsy tissue samples will be obtained and frozen in zinc-free tubes. Tissue samples will be dissolved in HCL and then analyzed for zinc. Blood and gastric fluid will also be analyzed after centrifugation by atomic absorption spectrophotometry.

PRIOR AND CURRENT PROGRESS

Serum, gastric fluid and biopsy tissue of 113 patients with endoscopic findings including esophagitis, gastritis, duodenal ulcer, or normal have been analyzed under this study to date. No new subjects were recruited this year as emphasis was placed on analyzing stored frozen samples.

CONCLUSIONS

The data show that with esophagitis, zinc concentrations significantly increase in esophageal tissue and significantly decrease in serum. A manuscript is in process.

REPORT DATE: 10/28/88

WORK UNIT # 1473

DETAIL SUMMARY SHEET

TITLE: Sucralfate Used as Adjunctive Therapy in Patients with Erosive Peptic Esophagitis Resulting from Gastroesophageal Reflux: A Random Double Blind Controlled Study

KEYWORDS: esophagitis, sucralfate, gastroesophageal reflux

PRINCIPAL INVESTIGATOR: Johnson, Lawrence COL MC

ASSOCIATES: Herrera, Jorge MD; Shay, Steven MD

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Completed  
APPROVAL DATE: Dec 1984

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To study the safety and effectiveness of carafate suspension to placebo when used as adjunctive therapy to Cimetidine in the therapy of erosive esophagitis.

TECHNICAL APPROACH

Patients with severe (grade 2 or more) erosive esophagitis were randomized to Carafate suspension vs. placebo suspension. They were seen monthly without repeat EGD and symptom rating. Compliance medications, improvement in symptoms and endoscopic esophagitis were assessed.

PRIOR AND CURRENT PROGRESS

A total of 38 patients were enrolled. Two withdrew voluntarily during the first week. Thirtysix patients completed the study. No significant side effects or complications were noted.

CONCLUSIONS

Thirtynine percent of patients on sucralfate and 11% of patients on placebo healed. P=1.127. No significant difference was noted in symptom improvement between the groups.

REPORT DATE: 12/15/88

WORK UNIT # 1478

DETAIL SUMMARY SHEET

TITLE: An Open Label Trial of the Long-term Therapy of Domperidone for Gastric Atony

KEYWORDS: gastric atony, domperidone

PRINCIPAL INVESTIGATOR: Shay, Steven COL MC

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Completed  
APPROVAL DATE: Jan 1986

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

Treatment of patients with gastric atony who cannot tolerate metoclopramide, the standard treatment for gastric atony.

TECHNICAL APPROACH

Open label therapeutic administration of Domperidone, and investigational drug provided at no cost to the government by Janssen pharmaceuticals. Patients take medication at lowest possible dose to minimize symptoms of gastric atony confirmed by gastric emptying studies.

PRIOR AND CURRENT PROGRESS

We have completed the study.

CONCLUSIONS

None to date.

REPORT DATE: 02/13/89

WORK UNIT # 1483

DETAIL SUMMARY SHEET

TITLE: Evaluation of Gastroesophageal Reflux as a Cause of Hoarseness

KEYWORDS: hoarseness, reflux, esophagitis

PRINCIPAL INVESTIGATOR: McNally, Peter MAJ MC

ASSOCIATES: Wong, Roy COL MC; Maydonovitch, Corinne BS

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Ongoing  
APPROVAL DATE: Apr 1986

FUNDING: Current FY: \$ 676 Previous FYs: \$ 1,653 Total: \$ 2,329

STUDY OBJECTIVE

Determine if Gastroesophageal reflux is a cause of "idiopathic" hoarseness.

TECHNICAL APPROACH

Patients with idiopathic hoarseness and characteristic ENT findings undergo standard GI evaluation for GERD. If GER is identified the patient undergoes baseline voice harmonic analysis which is re-evaluated after 8 weeks of medical therapy.

PRIOR AND CURRENT PROGRESS

Over a 10 month period, 120 of 2,000 (5%) outpatients were referred to an ENT physician for evaluation of hoarseness. Seventeen of these patients had idiopathic hoarseness and 11 of them were studied under this protocol. It was found that 6 or 55% had significant GE reflux and were placed on medical therapy. Even with therapy, the hoarseness did not significantly improve and therefore cannot be the sole source of hoarseness.

CONCLUSIONS

The results of this study show that severe GE Reflux is commonly seen in patients with idiopathic hoarseness and therefore it is reasonable to evaluate these patients in Gastroenterology. The findings of this study have been collated and a manuscript has been submitted for publication. Termination of study is pending acceptance for publication.

REPORT DATE: 02/22/89

WORK UNIT # 1484

DETAIL SUMMARY SHEET

TITLE: An Evaluation of Scintigraphy as a Gastroesophageal Reflux Test and its Comparative Value to Standard Testing Methods in Different Patient Groups within the Symptomatic Gastroesophageal Reflux Population

KEYWORDS: scintigraphy, reflux, gastroesophageal

PRINCIPAL INVESTIGATOR: Shay, Steven COL MC

ASSOCIATES: Agre, Susan

DEPARTMENT: Department of Medicine

STATUS: Completed

SERVICE: Gastroenterology Service

APPROVAL DATE: Apr 1986

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

Determine the normal range for frequency of scintigraphy reflux and clearance, and a comparison of normal volunteers to patients.

TECHNICAL APPROACH

Patients fill out a questionnaire to detail reflux symptoms. At the end of clinically indicated manometry pH monitoring, a test meal of commercial beef stew and a liquid radionuclide are ingested. Patients are monitored for 20 minutes in the recumbent position by Nuclear Medicine.

PRIOR AND CURRENT PROGRESS

The study was completed after enrolling 15 normal volunteers and 45 patients. The last patient was entered May 19, 1988.

CONCLUSIONS

The study is completed. The abstract entitled Scintigraphy in the Diagnosis of Gastroesophageal Reflux outlines the conclusions for this study.

REPORT DATE: 06/07/89

WORK UNIT # 1487

DETAIL SUMMARY SHEET

TITLE: Prospective Evaluation of the Effect of Medical Therapy on Plasma and Tissue Zinc Levels in Esophagitis

KEYWORDS: zinc, esophagitis, GERD

PRINCIPAL INVESTIGATOR: Wong, Roy COL MC

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Ongoing  
APPROVAL DATE: Jul 1986

FUNDING: Current FY: \$ 15 Previous FYs: \$ 1,143 Total: \$ 1,158

STUDY OBJECTIVE

a) Prospectively evaluate the effect of anti-gastroesophageal reflux therapy on plasma and esophageal tissue zinc concentrations; b) Determine if a correlation exists between degree of esophageal inflammation and plasma and esophageal zinc concentration.

TECHNICAL APPROACH

Patients with endoscopically proven peptic esophagitis undergo esophageal biopsy, and phlebotomy for tissue and serum zinc concentration. After standard medical anti-reflux therapy tissue and blood specimens are obtained for comparison zinc concentrations.

PRIOR AND CURRENT PROGRESS

A total of 12 patients have been studied under this protocol. However, due to technical difficulties in assaying for zinc concentration, no data have been acquired. No new patients were studied in the past year.

CONCLUSIONS

No conclusions can be drawn at this time.

REPORT DATE: 01/18/90

WORK UNIT # 1488

DETAIL SUMMARY SHEET

TITLE: *Campylobacter pyloridis*: Normal Flora or Pathogen

KEYWORDS: campylobacter pyloris, gram stain, Warthin starry stain

PRINCIPAL INVESTIGATOR: Holtzmuller, Kent MD

ASSOCIATES: Peura, David A. MD

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Terminated  
APPROVAL DATE: Aug 1986

FUNDING: Current FY: \$ 118 Previous FYs: \$ 650 Total: \$ 768

STUDY OBJECTIVE

Study has been undertaken to evaluate methodology in diagnosing *Campylobacter pyloris*. This has involved comparison of gram staining of gastric mucosa touch prep, Warthin starry staining, H & E, and culturing.

TECHNICAL APPROACH

A blinded prospective evaluation of gram stains of touch prep were compared with Warthin starry staining, H & E, and culture.

PRIOR AND CURRENT PROGRESS

One hundred and three subjects have been studied to date. Ongoing work is in progress to determine the occurrence of *Campylobacter* in gastric mucosa with the occurrence of gastritis and peptic ulcer disease. Patients with gastritis are now being entered into the study.

CONCLUSIONS

ADMINISTRATIVELY TERMINATED.

REPORT DATE: 05/02/89

WORK UNIT # 1489

DETAIL SUMMARY SHEET

TITLE: The Evaluation of Post prandial Supine Reflux Events by Simultaneous Esophageal Manometry, Esophageal pH Monitoring and Gastroesophageal Scintiscanning in Patients with Progressive Systemic Sclerosis with Severe Endoscopic Esophagitis

KEYWORDS: manometry, pH monitoring, scintigraphy scleroderma

PRINCIPAL INVESTIGATOR: McNally, Peter MAJ MC

ASSOCIATES: Shay, Steven COL MC; Abreu, Sue CPT MC

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Gastroenterology Service

APPROVAL DATE: Dec 1986

FUNDING: Current FY: \$ 312 Previous FYs: \$ 118 Total: \$ 430

STUDY OBJECTIVE

To determine whether the predominant pathophysiologic abnormality responsible for excessive esophageal exposure in patients with progressive systemic sclerosis (PSS) and severe endoscopic esophagitis is frequent reflux events, poor clearance of a few reflux events, or both.

TECHNICAL APPROACH

Patients with 1) endoscopic reflux esophagitis and abnormal 24 hour pH monitoring and 2) scleroderma form the study population. Simultaneous manometry (esophageal motor activity), scintigraphy (reflux volume) and pH monitoring are performed for 40 minutes after a test meal labelled with 1.0 m Cu 99m Tc sulfur colloid.

PRIOR AND CURRENT PROGRESS

A total of four patients have been studied to date. Each has shown abnormal clearance and frequent reflux events; however the former is a predominant abnormality. There have been no additional patients accrued in this protocol in the last year, due to the fact that these are not common patients.

CONCLUSIONS

We hope to enroll five or six more patients, although they are hard to find. If the results are consistent after two to three more patients, we will conclude the protocol. Therefore we request to continue the protocol in an ongoing status.

REPORT DATE: 04/03/89

WORK UNIT # 1490

DETAIL SUMMARY SHEET

TITLE: A Dose Response Study to Evaluate Safety and Efficacy of Ranitidine in Patients with Gastroesophageal Reflux Disease

KEYWORDS: gastroesophageal reflux, ranitidine, esophagitis

PRINCIPAL INVESTIGATOR: Herrera, Jorge MAJ MC

ASSOCIATES: Peura, David MD; Shay, Steven MD

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Completed  
APPROVAL DATE: Dec 1986

FUNDING: Current FY: \$ 95 Previous FYs: \$ 1,623 Total: \$ 1,718

STUDY OBJECTIVE

To evaluate the efficacy and safety of Ranitidine in patients that have symptomatic gastroesophageal reflux disease. Specifically we are assessing the efficacy of different dosages of Ranitidine in GER.

TECHNICAL APPROACH

Patients who have symptomatic GE reflux are enrolled in a two week basic evaluation where symptoms are assessed, the patient undergoes manometric and endoscopic studies. If the patient meets the criteria for the study they are randomized in a double-blind fashion into either placebo versus different dosages of Ranitidine given twice a day. Patients are followed on a monthly basis with a repeat endoscopy in three and six months and repeat manometric studies at the end of the study.

PRIOR AND CURRENT PROGRESS

We enrolled a total of 18 patients in the screening phase. Twelve of these patients have continued on the double-blind phase and completed the study. As of this date every patient has completed the study. The sponsoring company, Glaxo Inc., has requested that we stop enrolling patients in the study since they have reached the goal number of patients entered in the multicenter study.

CONCLUSIONS

A total of 18 patients was enrolled in the study. All of them completed the required evaluations. Data have been sent to Glaxo and they are analyzing the data from our center as well as all the other centers that participated in the study.

REPORT DATE: 12/11/89

WORK UNIT # 1491

DETAIL SUMMARY SHEET

TITLE: Use of Commercially Available Formulas for Feeding in Immediate Postoperative Period

KEYWORDS: nutrition, defined formula, postoperative

PRINCIPAL INVESTIGATOR: Sodhi, Parminder MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Completed  
APPROVAL DATE: Dec 1986

FUNDING: Current FY: \$ 42 Previous FYs: \$ 0 Total: \$ 42

STUDY OBJECTIVE

To assess the efficacy and palatability of commercially available formulas for feeding in the immediate postoperative period.

TECHNICAL APPROACH

Patients on the general surgery service, undergoing elective surgery, will be randomized (after informed consent) to receive either standard postoperative diet or feedings of Ensure (a commercially-available defined formula diet). Patient subsequently be assessed regarding daily protein and calorie intake as well as number of days until regular diet resumed. Palatability of each diet will also be assessed.

PRIOR AND CURRENT PROGRESS

A total of twenty-eight have been enrolled in this study. Fifteen patients received Ensure and thirteen patients received the standard post operative diet.

CONCLUSIONS

Caloric intake was equal in both groups on study days ( $559+94$  vs  $528+125$  SEM, Ensure vs control). Protein intake was greater in the Ensure group ( $18.9+3.4$  vs  $6.0+1.1$  gm/day, p 0.01). Patients receiving Ensure were advanced to regular diet sooner than those on standard diet alone ( $1.1+0.1$  vs  $1.6+0.3$  days, p=0.05).

REPORT DATE: 12/15/88

WORK UNIT # 1492

DETAIL SUMMARY SHEET

TITLE: Does Chronic Beta Carotene Alter the Response of Gastric Mucosa to Acute Aspirin Injury

KEYWORDS: gastric mucosa, aspirin, beta-carotene

PRINCIPAL INVESTIGATOR: Moses, Frank LTC MC

ASSOCIATES: Kikendall, J. LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Completed  
APPROVAL DATE: Feb 1987

FUNDING: Current FY: \$ 1,040 Previous FYs: \$ 0 Total: \$ 1,040

STUDY OBJECTIVE

To endoscopically evaluate and compare the severity of gastric mucosal damage induced by acute aspirin ingestion in patients receiving chronic B-carotene therapy or placebo.

TECHNICAL APPROACH

After baseline screening endoscopy patients given 2 ASA tablets and re-endoscoped 3 hours later. Scoring is by visual scale. Serum ASA level is taken and questionnaire administered.

PRIOR AND CURRENT PROGRESS

Fifteen subjects entered and three were eliminated from the study. Data from twelve subjects were analyzed statistically. The protocol was terminated because no therapeutic trends were noted. B-carotene did not appear to offer protection to the gastric mucosa from the effects of aspirin injury.

CONCLUSIONS

The study was terminated and no further patients will be enrolled.

REPORT DATE: 05/10/89

WORK UNIT # 1493

DETAIL SUMMARY SHEET

TITLE: A Study to Evaluate the Development of Quantitative Analysis of Video-digital Images Obtained During Esophagogastroduodenoscopy

KEYWORDS: videoendoscopy

PRINCIPAL INVESTIGATOR: Moses, Frank LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Ongoing  
APPROVAL DATE: Jun 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To develop an image collecting procedure that will permit quantitative image analysis. To develop disease oriented quantitative image analysis. To evaluate the utility of quantitative image analysis in endoscopic diagnosis of GI disease.

TECHNICAL APPROACH

This is a multicenter protocol. This institution along with others has the primary task of obtaining endoscopic photographs taken with videodigital technology of esophageal erosions and duodenal ulcers. These photographs are stored in computer format and sent to a separate center for further analysis of size, shape, and other topographic characteristics.

PRIOR AND CURRENT PROGRESS

Twenty-four subjects entered, 18 for lack of suitable endoscopic pathology. Six subjects had photographs recorded in stated manner, standard forms completed and records sent. During the past year, no further subjects have been entered. The multicenter organizers have temporarily postponed further work on this protocol pending redevelopment of photographic and computer hardware used in the system. No restart date has been given as of this time.

CONCLUSIONS

None to date.

REPORT DATE: 04/25/89

WORK UNIT # 1494

DETAIL SUMMARY SHEET

TITLE: Effect of Hypertonic Phosphate (Fleets) and Colyte Colonic Enemas on Venous pH, Osmolality, Serum Calcium, Phosphate, and Electrolytes in Patients Undergoing Flexible Sigmoidoscopy

KEYWORDS: flexible sigmoidoscopy, fleet enemas, metabolic changes

PRINCIPAL INVESTIGATOR: Lyons, Michael CPT MC

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Completed  
APPROVAL DATE: Jun 1987

FUNDING: Current FY: \$ 355 Previous FYs: \$ 0 Total: \$ 355

STUDY OBJECTIVE

Evaluate the metabolic effects following colonic administration of Fleet hypertonic phosphate enemas.

TECHNICAL APPROACH

Draw blood samples before and after Fleet enema administration and analyze blood changes in electrolytes, calcium, phosphate and venous pH.

PRIOR AND CURRENT PROGRESS

Thirty-one patients with grossly normal colonic mucosa and 13 patients with known idiopathic ulcerative colitis were studied under this protocol. Blood samples were drawn for measurement of electrolytes, Ca++, phosphorus and pH before and immediately after self administering 2 consecutive Fleet hypertonic phosphate enemas (HPE's).

CONCLUSIONS

Colonic absorption of phosphate found in HPE's can lead to hyperphosphatemia and acidemia in patients with normal colonic mucosa and patients with ulcerative colitis. These data suggest caution when using HPE's in patients with inflammatory colonic states, renal disease or acid-base disorders.

REPORT DATE: 10/18/88

WORK UNIT # 1495

DETAIL SUMMARY SHEET

TITLE: Effect of Beta-Carotene on Mucosal Proliferation in Patients with Colonic Carcinoma

KEYWORDS: beta-carotene, colon carcinoma, proliferation

PRINCIPAL INVESTIGATOR: Phillips, Raymond MAJ MC

ASSOCIATES: Wong, Roy COL MC, Kikendall, James LTC MC

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Gastroenterology Service

APPROVAL DATE: Oct 1987

FUNDING: Current FY: \$ 2,038

Previous FYs: \$

0

Total: \$ 2,038

STUDY OBJECTIVE

To determine the effect of beta carotene on colonic epithelial proliferation in patients with resected adenocarcinoma of the colon or rectum.

TECHNICAL APPROACH

Patients with previously resected colon carcinoma are studied prior to and at 2, 9, 16, 24, and 28 weeks after receiving beta-carotene, 30mg PO QD. At each time point, biopsies and blood samples are obtained. Rectal mucosal biopsies are assayed for cell proliferation by tritiated thymidine uptake and ODC levels. Blood samples are analyzed for beta carotene levels.

PRIOR AND CURRENT PROGRESS

Fifteen subjects have been accessed into the study and are being studied at the various time points while on beta-carotene. There have been no withdrawals from the study and no adverse reactions to beta-carotene. Samples are being collected and stored for analysis.

CONCLUSIONS

Subjects are currently being enrolled in the study. No data from blood or biopsy samples have been obtained to date.

REPORT DATE: 10/19/88

WORK UNIT # 1496

DETAIL SUMMARY SHEET

TITLE: The Effects of Non-Steroidal Anti-Inflammatory Drugs on the Secretion of Human Salivary Epidermal Growth Factor

KEYWORDS: epidermal growth factor, nonsteroidal drugs, salivary

PRINCIPAL INVESTIGATOR: Wong, Roy COL MC

ASSOCIATES: Maydonovitch, Corinne BS; Dutta, Sudhi MD

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Ongoing  
APPROVAL DATE: Oct 1987

FUNDING: Current FY: \$ 503 Previous FYs: \$ 0 Total: \$ 503

STUDY OBJECTIVE

To determine if therapeutic doses of non-steroidal anti-inflammatory drugs affect salivary epidermal growth factor secretion in humans.

TECHNICAL APPROACH

In a double blind manner, subjects will receive, at separate occasions two weeks apart, placebo TID for 3 days of indomethacin 50mg TID for 3 days and a final dose on the morning of saliva collection. Baseline saliva samples will be collected in an unstimulated and stimulated fashion prior to ingestion of placebo or indomethacin and again 2 hours after the last dose of placebo or indomethacin. At the time of each saliva collection, blood samples will be drawn to monitor indomethacin levels.

PRIOR AND CURRENT PROGRESS

Twenty subjects have been accessioned into the study. No subjects dropped out of the study. Saliva and blood samples were collected on all subjects before and after placebo and indomethacin. Samples are currently being analyzed for indomethacin, EGF and protein concentrations.

CONCLUSIONS

Results are pending sample analysis.

REPORT DATE: 11/21/88

WORK UNIT # 1497

DETAIL SUMMARY SHEET

TITLE: The Effect of Indomethacin on Rectosigmoid Mucosal Blood Flow and Rectosigmoid Mucosal Prostaglandin Levels in Humans

KEYWORDS: indomethacin, rectosigmoid, lazer doppler

PRINCIPAL INVESTIGATOR: Holtzmuller, Kent MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Ongoing  
APPROVAL DATE: Oct 1987

FUNDING: Current FY: \$ 1,250 Previous FYs: \$ 0 Total: \$ 1,250

STUDY OBJECTIVE

To determine the effect of prostglandin synthesis inhibition on rectosigmoid mucosal blood flow and rectosigmoid mucosal prostaglandin E2 levels.

TECHNICAL APPROACH

In a double blind, randomized fashion, each subject will receive, on two separate occasions separated by two weeks, either placebo TID for 3 days or indomethacin, 50mg TID for three days. The morning after the final dose of placebo or indomethacin, rectosigmoid mucosal blood flow will be measured with a lexer-doppler probe inserted through the biopsy channel of an endoscope. Two rectal mucosal biopsies will also be obtained for tissue prostaglandin levels and blood sample for indomethacin levels.

PRIOR AND CURRENT PROGRESS

A pilot study of 5 subjects has been completed to establish reproducibility of measurement of rectomucosal blood flow on two separate days. The study is progressing to phase II where subjects will be studied in two separate occasions after taking placebo or indomethacin.

CONCLUSIONS

A pilot study of 5 subjects has been completed. The data show that rectomucosal blood flow can be reproducibly obtained on two separate occasions utilizing a laser-doppler probe passed through an endoscope.

REPORT DATE: 11/25/88

WORK UNIT # 1498

DETAIL SUMMARY SHEET

TITLE: Pathophysiology and Treatment for Non-Ulcer Dyspepsia (Using Cisapride)

KEYWORDS: non-ulcer dyspepsia, irritable bowel syndrome, cisapride

PRINCIPAL INVESTIGATOR: Keate, Ray MAJ MC

ASSOCIATES: Shay, Steven COL MC; Maydonovitch, Corrine BS

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Ongoing  
APPROVAL DATE: Dec 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To compare gastric motility and electrophysiology in patients with non-ulcer dyspepsia vs. normal volunteers. To determine the effect of a prokinetic agent, Cisapride, on symptoms and objective tests in patients with non-ulcer dyspepsia in a double-blind crossover placebo controlled fashion.

TECHNICAL APPROACH

Patients with dyspeptic symptoms in whom ulcer has been rigorously excluded are studied. Three hour electrogastrograms and 24 hour antral motility evaluations are performed after treatment with placebo and cisparide. Changes in symptoms are measured using a questionnaire. A double-blind crossover design is employed so that each subject receives both placebo and cisapride.

PRIOR AND CURRENT PROGRESS

No subjects have been enrolled. Part of the reason for this is that the study design and consent form had to be modified following reports of seizures and dyskinesia with Cisapride. Active recruitment is presently underway.

CONCLUSIONS

All revisions have been accomplished. No data is available because no patients have been enrolled.

REPORT DATE: 04/25/89

WORK UNIT # 1499

DETAIL SUMMARY SHEET

TITLE: The Effects of IV Ranitidine on Gastric pH in Patients Undergoing Vascular Surgery: An Evaluation of Dose for Effective pH Control

KEYWORDS: IV Ranitidine, gastric pH, vascular surgery

PRINCIPAL INVESTIGATOR: Stann, Carl MAJ MC  
ASSOCIATES: Holtzmuller, Kent CPT MC

DEPARTMENT: Department of Medicine  
SERVICE: Gastroenterology Service

STATUS: Ongoing  
APPROVAL DATE: Jan 1988

FUNDING: Current FY: \$ 1,768      Previous FYs: \$ 0      Total: \$ 1,768

STUDY OBJECTIVE

a) To determine the effective dose of IV ranitidine which is necessary to maintain intragastric pH at 4 or greater. b) To determine the length of time that gastric pH can be maintained at pH4 or greater following a specific dose of ranitidine.

TECHNICAL APPROACH

Forty patients undergoing surgical reconstruction of the abdominal aorta for advanced atherosclerotic vascular disease or for aortic aneurysm formation will be studied. During surgery, an NG tube with antimony pH probe will be passed nasally and positioned in the stomach. After surgery, intragastric pH will be monitored and recorded hourly.

PRIOR AND CURRENT PROGRESS

Progress to date includes setting up working area in SICU to process blood samples collected to monitor serum ranitidine levels and interfacing antimony electrode with standardized 24 hour monitoring system intragastric. Two patients have been considered but excluded from study.

CONCLUSIONS

None.

REPORT DATE: 03/28/89

WORK UNIT # 1012

DETAIL SUMMARY SHEET

TITLE: A Study of the Effects on Patient Satisfaction of Teaching Interviewing Skills to Medical Residents

KEYWORDS: medical interviewing, patient satisfaction, medical education

PRINCIPAL INVESTIGATOR: Weaver, Michael LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: General Medicine Service

STATUS: Completed  
APPROVAL DATE: May 1985

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine whether teaching medical residents interviewing skills results in increased patient satisfaction in the Internal Medicine Clinic.

TECHNICAL APPROACH

A randomized controlled trial comparing five hours of interviewing skills instruction with a similar amount of biomedical instruction. Patient satisfaction was measured using the residents' own clinic patients. Interviewing skills were measured using videotaped interviews with standardized simulated patients (SSP), evaluated by blinded raters using a newly developed rating scale.

PRIOR AND CURRENT PROGRESS

1) Medical residents have significant weaknesses and deficits in their interviewing skills which can be easily and reproducibly measured using the videotape rating technique we have devised. 2) The internal medicine residents we studied have lower overall psychosocial values and skills than practicing internists and family practitioners. However, in this study there is no correlation between the residents' attitudes and values, their interviewing skills, and their patients' satisfaction. 3) Patient satisfaction with their residents was high in spite of their residents significant interviewing limitations and relatively low psychosocial values and attitudes.

CONCLUSIONS

1) Medical residents have significant weaknesses and deficits in their interviewing skills which can be easily and reproducibly measured using the videotape rating technique we have devised. 2) The internal medicine residents we studied have lower overall psychosocial values and skills than practicing internists and family practitioners. However, in this study there was no correlation between the residents' attitudes and values, interviewing skills, and patients' satisfaction.

REPORT DATE: 07/10/89

WORK UNIT # 1016

DETAIL SUMMARY SHEET

TITLE: A Linguistic Analysis of Resident-Patient Interaction

KEYWORDS: linguistic, interview, communication

PRINCIPAL INVESTIGATOR: Harvey, Joan LCDR MC USN

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: General Medicine Service

APPROVAL DATE: Aug 1986

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To investigate how the use of linguistic forms that are associated with male/female language affect doctor/patient communication.

TECHNICAL APPROACH

Previously made videotapes of residents interviewing simulated patients will be transcribed, and the interview analyzed for the use of certain linguistic features. There is no substantial modification to the original protocol.

PRIOR AND CURRENT PROGRESS

All of the tapes have been transcribed data has been checked. Statistical analysis has begun and is about 25% completed.

CONCLUSIONS

REPORT DATE: 10/04/89

WORK UNIT # 1017

DETAIL SUMMARY SHEET

TITLE: Alkaline Phophatase Abnormalities in Hip Fractures

KEYWORDS: alkaline phosphotase, hip fracture

PRINCIPAL INVESTIGATOR: Steinweg, Donald MAJ MC

DEPARTMENT: Department of Medicine

STATUS: Completed

SERVICE: General Medicine Service

APPROVAL DATE: Nov 1986

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To define the range and origin of alkaline phosphotase elevations after hip fracture.

TECHNICAL APPROACH

Blood drawing every 5 days for total of 4 samples per patient.

PRIOR AND CURRENT PROGRESS

Fifteen patients were studied; no adverse effects occurred.

CONCLUSIONS

Elevated alkaline phosphotase levels that occur prior to day eleven after hip surgery are all due to liver origin.

REPORT DATE: 12/07/89

WORK UNIT # 1019

DETAIL SUMMARY SHEET

TITLE: Clinical Competence Assessment of Internal Medicine Residents Using a Multistep Examination of Diagnosis and Management Skills and a Videotaped Review of Interpersonal Skills

KEYWORDS:

PRINCIPAL INVESTIGATOR: Jeffers, Duane MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: General Medicine Service

STATUS: Terminated  
APPROVAL DATE: Oct 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

ADMINISTRATIVELY TERMINATED.

TECHNICAL APPROACH

ADMINISTRATIVELY TERMINATED.

PRIOR AND CURRENT PROGRESS

ADMINISTRATIVELY TERMINATED.

CONCLUSIONS

ADMINISTRATIVELY TERMINATED.

REPORT DATE: 12/07/89

WORK UNIT # 1020

DETAIL SUMMARY SHEET

TITLE: History Taking in the Internal Medicine Context: Observation of Resident Skills

KEYWORDS:

PRINCIPAL INVESTIGATOR: Diemer, Margretta MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: General Medicine Service

STATUS: Terminated  
APPROVAL DATE: Oct 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

ADMINISTRATIVE TERMINATION.

TECHNICAL APPROACH

ADMINISTRATIVE TERMINATION

PRIOR AND CURRENT PROGRESS

ADMINISTRATIVE TERMINATION

CONCLUSIONS

ADMINISTRATIVELY TERMINATED.

REPORT DATE: 08/02/89

WORK UNIT # 1021

DETAIL SUMMARY SHEET

TITLE: Evaluation of Patient Utilities for Cholesterol Lowering Therapy

KEYWORDS: hypercholesterolemia, decision analysis

PRINCIPAL INVESTIGATOR: Reed, William MAJ MC

DEPARTMENT: Department of Medicine

STATUS: Completed

SERVICE: General Medicine Service

APPROVAL DATE: Aug 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

We undertook to evaluate the values and preferences of patients currently on therapy for hypercholesterolemia, using standard techniques of decision analysis.

TECHNICAL APPROACH

After informed consent, we used a questionnaire to record patients' background and coronary risk factors. We used a structured interview to evaluate their preferences related to therapy and risk of disability, using the time-tradeoff and standard reference gamble methods.

PRIOR AND CURRENT PROGRESS

We have completed data collection, having enrolled 35 patients into the study. There have been no patient-related problems, except mild transient anxiety in some patients. We do not anticipate any direct benefit to patients.

CONCLUSIONS

Evaluation of the data after 19 patients had been enrolled revealed considerable variability in patient preferences. This variability is likely to be very important in determining the most appropriate physician approach to hypercholesterolemia in selected patients.

REPORT DATE: 04/06/89

WORK UNIT # 1602-81

DETAIL SUMMARY SHEET

TITLE: Regulation of Granulopoiesis In Vitro Incorporation of <sup>14</sup>C-Glucosamine in Normal Human Bone Marrow Granulocytes with Patients' Sera with Primary and Secondary Bone Marrow Granulocyte Disorders

KEYWORDS: granulopoiesis, regulation, granulocytes

PRINCIPAL INVESTIGATOR: Ward, Frank MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Hematology-Oncology Service

STATUS: Ongoing  
APPROVAL DATE: May 1981

FUNDING: Current FY: \$ 549 Previous FYs: \$ 5,626 Total: \$ 6,175

STUDY OBJECTIVE

a) Purification of stimulators and inhibitors that are responsible for the regulation of granulopoiesis; b) To identify the site of <sup>14</sup>C-glucosamine incorporation within the granulocytic precursor cell membrane, primary and secondary granules.

TECHNICAL APPROACH

Mature and immature granulocytes are prepared from blood and bone marrow. From some preparations membranes and granules are prepared. The whole cell and its subcellular fractions extracts are studied for their proteins - maturation markers - by High Performance Liquid Chromatography and electrophoretic separations. Serum is collected and evaluated for the rate of granulocytic maturation by applying it, or its partially purified fractions, to cell cultures of immature granulocytes. Morphological and biochemical assays are plotted graphically.

PRIOR AND CURRENT PROGRESS

We have tested inflammatory sera and have detected a significant difference between inflammatory sera from normal on the effect of cell division and maturation. We have developed procedures for isolating early immature cells from human bone marrow and growing them in cultures with our serum or its fractions. We are working on purification of our "maturation" factor from human sera by using a variety of chromatographic techniques, including monoclonal and polyclonal antibodies against a postulated part of our protein complex purif. approximately 1000 fold. Additional 19 donated cells and serum which were then studied in the cultures. The culture well is the unit of study in these experiments. There are no experiments in this study involving human subjects other than donating blood or bone. No adverse reactions. No direct benefit.

CONCLUSIONS

Inflammatory conditions (sepsis) block inhibitors which control granulopoiesis which accounts for leukocytosis during infection. A protein marker was identified after blast stages and disappearing in mature, circulating granulocytes. This marker is attached to mature CML cells. Immature human granulocytes can be maintained in our serum free cell culture for 8 days without significant division, maturation by our human serum preparation.

REPORT DATE: 08/25/89

WORK UNIT # 1616-82

DETAIL SUMMARY SHEET

TITLE: Phenotypic Characterization of Granulocytic Leukemia Blast Cells by High Performance Liquid Chromatographic Analysis of Cellular Proteins

KEYWORDS: CML, protein analysis, HPLC +electrophoresis

PRINCIPAL INVESTIGATOR: Bednarek, Jana MD

ASSOCIATES: Knight, Robert LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Hematology-Oncology Service

STATUS: Ongoing  
APPROVAL DATE: Sep 1982

FUNDING: Current FY: \$ 428 Previous FYs: \$ 1,716 Total: \$ 2,144

STUDY OBJECTIVE

Do granulocytes, mature and immature, circulating in blood or obtained from bone marrow, contain any phenotypic marker proteins as determined by HPLC and electrophoresis (and possibly immunochemical methods) that might serve as clinical indicators for: a) classifying CML patients into prognostic and therapeutic categories, b) predicting the onset of blast crisis, c) early diagnosis.

TECHNICAL APPROACH

Mature and immature granulocytes obtained from normal volunteer blood or bone marrow or peripheral blood from CML patients in different stages of their disease were prepared with purity better than 90%, as described previously. In select preparations we also prepared subcellular fractions. Proteins were extracted, as described previously, and separated by reverse phase HPLC and SDS slab gel electrophoresis of HPLC fractions. A pattern of select proteins were followed with the progression of the disease.

PRIOR AND CURRENT PROGRESS

We developed a method which allows us to study qualitatively and semiquantitatively large number of proteins contained in different parts of the cell. We studied granulocytes from peripheral blood of 29 CML patients, 25 healthy volunteers and 9 others with bone marrow diseases which served as controls. CML patients were followed over a period of time, as they were returning for treatments. We followed two patients from 1988, one on interferon treatment, and one that has a mosaic chromosome Ph+ (still in stable phase; her normal stem cells are successfully competing with the Ph+ ones). No additional patients added this year (our work was included in the Yearbook of Medical Publishers 1989).

CONCLUSIONS

A pattern of proteins separated by our method of use of HPLC and SDS electrophoresis, was shown to be common and very stable for normal granulocytes (male and female, ages 19 to 70, mature granulocytes from normal peripheral blood served as our controls). For CML patients this pattern is different and varies with the stage of the disease. Specific proteins emerged as markers.

REPORT DATE: 01/03/89

WORK UNIT # 1638-86

DETAIL SUMMARY SHEET

TITLE: WRAMC 8602 Clinical Pharmacokinetic (Phase I) Study of Hexamethylene Bisacetamide in Patients with Advanced Solid Tumors

KEYWORDS: hexamethylene, bisacetamide

PRINCIPAL INVESTIGATOR: Ward, Frank MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Hematology-Oncology Service

STATUS: Ongoing  
APPROVAL DATE: Feb 1986

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To evaluate toxicities and determine the maximum tolerated dose of HMBA given via nasogastric tube and orally in tablet form in patients with previously treated but refractory malignancies or previously untreated malignancies for which no curative therapy exists. The pharmacokinetics of HMBA given either method include studies of plasma urine.

TECHNICAL APPROACH

Non-randomized study in which all eligible patients receive HMBA first by nasogastric tube, and thereafter by oral tablet form. Doses have escalated to 6000mg/m<sup>2</sup> to date.

PRIOR AND CURRENT PROGRESS

To date a total of 21 patients have been entered. Study is still open to patient entry. Two patients have been entered at that dose level then escalation will be continued until maximum tolerated dose is achieved.

CONCLUSIONS

Therapy via nasogastric tube has comparable toxicity as seen by oral ingestion at the same daily dose. Gastrointestinal and neurotoxicity were noted at higher doses. Maximum tolerated dosage has not yet been reached. To date no objective tumor response at these drug levels has been seen.

REPORT DATE: 02/17/89

WORK UNIT # 1639-86

DETAIL SUMMARY SHEET

TITLE: Characterization of Human Antineutrophil Antibodies

KEYWORDS: neutropenia, anti-neutrophil, autoantibodies

PRINCIPAL INVESTIGATOR: Wright, Daniel LTC MC

ASSOCIATES: Hartman, Kip MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Hematology-Oncology Service

STATUS: Ongoing  
APPROVAL DATE: Mar 1986

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To characterize the neutrophil antigens recognized by naturally occurring anti-neutrophil antibodies in autoimmune neutropenia.

TECHNICAL APPROACH

Sera from patients with neutropenia of suspected autoimmune origin are screened for the presence of anti-neutrophil antibodies. Further studies are then performed to further characterize these antibodies, including Western Blotting, affinity chromatography separation of suspected autoantibodies, and immunofluorescence studies of autoantibody activity.

PRIOR AND CURRENT PROGRESS

Sera from 8 of 36 patients with autoimmune neutropenia were found to have antibody to a 43 kD neutrophil membrane-associated protein that we identified as actin. Purified IgG and F(ab')<sup>2</sup> fragments also bound to this protein in immunoblots confirming antigen-antibody specific binding. An affinity purified human anti-actin immunoglobulin was prepared from the serum of one of the index patients; this IgG retained anti-neutrophil antibody reactivity when tested with intact neutrophils. The 8 patients with anti-actin antibody tended to have "strongly positive" anti-neutrophil antibody reactivity, and tended to be more severely neutropenic than other patients with autoimmune neutropenia.

CONCLUSIONS

More than 20% of patients with neutropenia and anti-neutrophil antibodies had antibodies to a 43 KD neutrophil membrane-associated protein that we identified as actin. The significance of anti-actin autoantibodies in patients with autoimmune neutropenia deserves further study.

REPORT DATE: 10/18/88

WORK UNIT # 1644-87

DETAIL SUMMARY SHEET

TITLE: Chromosomal Radiosensitivity During the G2 Cycle Period of Normal Lymphocytes from Individuals with Malignant Lymphoma: A Pilot Study

KEYWORDS: chromosomal, radiosensitivity, lymphoma

PRINCIPAL INVESTIGATOR: Knight, Robert LTC MC

ASSOCIATES: Bednarek, Jana PhD

DEPARTMENT: Department of Medicine  
SERVICE: Hematology-Oncology Service

STATUS: Completed  
APPROVAL DATE: Oct 1986

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine if there is an increase in chromosomal fragility in the peripheral blood lymphocytes of patients with malignant lymphoma.

TECHNICAL APPROACH

Lymphocytes are isolated from peripheral blood and subjected to 100R of irradiation. The cells are then mixed with RPMI-1640 and 15% FBS. Subsequently colcemid is added to arrest cells in mitosis. The cells are then fixed and the number of chromosomal gaps and breaks per 100 cells are counted.

PRIOR AND CURRENT PROGRESS

A total of 16 subjects have been enrolled. None have been withdrawn. No differences in the chromosomal fragility of peripheral blood lymphocytes were found between normal subjects and those with malignant lymphoma.

CONCLUSIONS

This technique did not detect an increase in chromosomal fragility in the peripheral blood lymphocytes of patients with malignant lymphoma.

REPORT DATE: 03/31/89

WORK UNIT # 1647-87

DETAIL SUMMARY SHEET

TITLE: The Value of Electronic Platelet Sizing in the Evaluation of Thrombocytopenia

KEYWORDS: platelet, size, thrombocytopenia

PRINCIPAL INVESTIGATOR: Vukelja, Svetislava CPT MC

DEPARTMENT: Department of Medicine  
SERVICE: Hematology-Oncology Service

STATUS: Completed  
APPROVAL DATE: May 1987

FUNDING: Current FY: \$ 250 Previous FYs: \$ 0 Total: \$ 250

STUDY OBJECTIVE

The purpose of this study is to correlate the three electronic estimates of platelet size (MPV, PDW, megathrombocyte count) with the microscopic estimate of platelet size. The second purpose is to test the sensitivity and specificity of these electronic platelet sizing parameters in thrombocytopenia.

TECHNICAL APPROACH

Thrombocytopenic patients are studied. Electronic determination mean platelet volume (MPV) and platelet distribution curve are made. Microscopic determination of platelet number, mean platelet size and percentage of megathrombocytes is made. A correlation coefficient for electronic vs manual platelet number, size, and percentage of megathrombocytes is made. The sensitivity and specificity are calculated.

PRIOR AND CURRENT PROGRESS

Total of 217 patients were studied. The study is closed at this time. No patients experienced any adverse effect. MPV may benefit some patients because of high specificity by supporting other data on hand. However it is not a sensitive test.

CONCLUSIONS

MPV, PDW platelet mass and megathrombocyte percent correlate poorly with the state of platelet production. MPV is specific (93%) but not a sensitive (39%) test. Positive and negative predictive values are poor.

REPORT DATE: 08/21/89

WORK UNIT # 1648-87

DETAIL SUMMARY SHEET

TITLE: WRAMC 8701 The Genetic Correlates of Multidrug Resistance in Human  
Tumors: A Collaborative NCI-WRAMC Pilot Study

KEYWORDS: multidrug, resistance, tumors

PRINCIPAL INVESTIGATOR: Reid, Thomas MAJ MC  
ASSOCIATES: Schuyler, Newman

DEPARTMENT: Department of Medicine  
SERVICE: Hematology-Oncology Service

STATUS: Completed  
APPROVAL DATE: Jul 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

The purpose of this study is to analyze tissue specimens from a variety of human malignancies for evidence of markers of multidrug resistance. Cell cultures of malignant cells exhibit variable sensitivity to chemotherapeutic agents. Moreover, cell cultures exposed to chemotherapeutic agents often become resistant to those drugs as well as other drugs. Various markers, including the p170 glycoprotein and glutathione transferase are examined in tissue from human tumors.

TECHNICAL APPROACH

After obtaining informed consent, the tumor specimen is examined with the assistance of the frozen section pathologist. Tumor not needed for diagnosis or to determine margins is then obtained in approximately one gram quantities, quick frozen in isopentane, then examined in the Clinical Pharmacology Branch of the National Cancer Institute with standard biochemical and molecular biology techniques including Western blots and Northern blots for evidence of levels of genes or gene expression. There have been no modifications to the original protocol.

PRIOR AND CURRENT PROGRESS

Since the initiation of the protocol, 12 patients have been entered onto this protocol and signed the consent form. Tumor specimens were obtained and processed on 7 of these patients and transported to the NCI where the laboratory evaluation is underway. In the cases of the other patients, either tumor could not be obtained due to the unresectable nature of the malignancy, or there were scheduling problems which precluded the collection of tumor specimens (surgery cancellations, etc.) There have been no adverse reactions or effects on patients. As expected, there have been no direct benefits to the patients.

CONCLUSIONS

This protocol is closed at of the date of this report. Unfortunately, Dr. Wall has had no activity in the past year. No data was gathered and thus no results will be forthcoming.

REPORT DATE: 08/25/89

WORK UNIT # 1649-87

DETAIL SUMMARY SHEET

TITLE: Molecular Basis of the Maturation of Bone Marrow Granulocytes: A Pilot Study of the Isolation and Purification of Granulocyte Maturation Regulators from Normal Human Serum

KEYWORDS: neutrophilic granulocyte, maturation factor, human serum

PRINCIPAL INVESTIGATOR: Bednarek, Jana PhD

ASSOCIATES: Knight, Robert LTC MC

DEPARTMENT: Department of Medicine

SERVICE: Hematology-Oncology Service

STATUS: Ongoing

APPROVAL DATE: Sep 1987

FUNDING: Current FY: \$ 2,992 Previous FYs: \$ 0 Total: \$ 2,992

STUDY OBJECTIVE

To determine if normal granulocyte precursors obtained from human bone marrow undergo maturation in vitro in the presence of normal human serum. Subsequently, chromatographic fractions of serum will be used to isolate and characterize the maturation inducing activity.

TECHNICAL APPROACH

We isolate early granulocytic precursor cells from bone marrow aspirate obtained from normal human volunteers, by a series of differential and density gradient centrifugations. These precursor cells are then put into culture wells where they are exposed to varying concentrations of human serum, its fraction as we attempt to purify the activity, and also trace metals, C vitamin, for a period of 2-8 days under 95% air and 5% CO<sub>2</sub> in the incubator. Cells are then examined for their appearance, the degree of maturity, by staining them on glass plates and examining them under microscope and alkaline phosphatase assay.

PRIOR AND CURRENT PROGRESS

We found human serum activity that triggers the end-stage maturation of normal human early granulocytic precursor cells in liquid culture assay system. Induction of morphological maturation is dose dependent up to 5% of serum, with pronounced inhibition at higher concentration. Inhibitor was removed on DEAE-Fractogel 650S in phosphate buffer 0.01M(pH7.0) where the reactivity was bound to be later removed by a gradient of NaCl. The activity was further purified on size exclusion column where it appeared to have MW over 3000. Transferrin plays supportive role. Activity cannot be substituted by granulocyte colony stimulating factor. Activity is relatively stable at pH 8.6 and 5.5 and this was used to further purify the activity on ion exchange columns to approximately 1000x. It now appears to be approximately 80,000 MW. Activity is easily lost on freezing, dialysis and concentration sticks to materials.

CONCLUSIONS

There is an activity in normal human serum that triggers the end-stage maturation of normal human granulocytic precursor cells into polymorphonuclear cells as well as by appearance of alkaline phosphatase activity.

REPORT DATE: 01/17/90

WORK UNIT # 1650-87

DETAIL SUMMARY SHEET

TITLE: Exploratory Dose Finding Study to Assess the Efficacy and Safety of Intravenous AHR 11190B (Zacopride Hydrochloride) in the Prevention of Cisplatin-Induced Emesis

KEYWORDS: zacopride hydrochloride, IND, drug

PRINCIPAL INVESTIGATOR: Lombardo, Fredric MAJ MS

DEPARTMENT: Department of Medicine  
SERVICE: Hematology-Oncology Service

STATUS: Ongoing  
APPROVAL DATE: Nov 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To assess the efficacy and safety of single doses of zacopride hydrochloride in the prevention of cisplatin-induced emesis and to investigate the dose-response effect of zacopride hydrochloride for prevention of emesis caused by cisplatin.

TECHNICAL APPROACH

Protocol outline methodology. A particular dose of zacopride is given 30 minutes prior to cisplatin infusion. If patients have six or more emetic episodes; Zopacide would be considered a filum; and other antiemetics will be administered.

PRIOR AND CURRENT PROGRESS

A.H. Robins Company has decided to suspend this particular protocol since the first 10 patients placed on the protocol experienced nausea and vomiting prior to any chemotherapy. No patient has been placed on this protocol at this institution.

CONCLUSIONS

Would desire to keep the protocol open with the anticipation that collaborators at the A.H. Robins Company could decrease the side effects of the agent. No patient will be placed on this protocol until amendments are made.

REPORT DATE: 06/28/88

WORK UNIT # 1651-88

DETAIL SUMMARY SHEET

TITLE: A Retrospective Comparison of Magnetic Resonance Imaging and Myelography to Detect Spinal Metastases and Epidural Cord Compression

KEYWORDS:

PRINCIPAL INVESTIGATOR: Redmond, John COL MC

DEPARTMENT: Department of Medicine  
SERVICE: Hematology-Oncology Service

STATUS: Completed  
APPROVAL DATE: Mar 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

Retrospective blind comparison of spinal myelography versus MR in the detection of epidural metastases.

TECHNICAL APPROACH

Goal was to identify 50 patients with cancer over the past three years who had undergone both spinal myelography and MR. Radiologists would then blindly interpret both studies for epidural metastases.

PRIOR AND CURRENT PROGRESS

During case finding phase we were only able to identify 15 patients who met above criteria and had imaging studies which could be found in the Radiology Department.

CONCLUSIONS

Study cannot be done and is terminated.

REPORT DATE: 02/27/89

WORK UNIT # 1652-88

DETAIL SUMMARY SHEET

TITLE: HLA Typing in a Sibship with Two Brothers with Hairy Cell Leukemia

KEYWORDS: sibling, leukemia, hairy cell

PRINCIPAL INVESTIGATOR: Ward, Frank MAJ MC

ASSOCIATES: Baker, James MAJ MC; Dow, Nancy MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Hematology-Oncology Service

STATUS: Completed  
APPROVAL DATE: Mar 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

a) Identify HLA haplotypes of sibship; b) identify whether the two affected siblings share HLA haplotypes with each other or with previously reported cases of HLA-associated hairy cell leukemia.

TECHNICAL APPROACH

Blood samples were submitted for HLA typing, complete blood count with platelet count and differential, TRAP staining of buffy coat cells. Personal and medical histories were obtained by one of the investigators. The results were analyzed in this descriptive study.

PRIOR AND CURRENT PROGRESS

Study has been completed and manuscript has been submitted to CANCER. Four Volunteers enrolled. No benefit to patients.

CONCLUSIONS

Hairy cell leukemia is not associated with a specific HLA antigen. HLA typing in familial hairy cell leukemia supports dominant inheritance of a predisposition for the disease in affected families. Variable penetrance or additional environmental or genetic factors affect disease development in at-risk individuals.

REPORT DATE: 02/14/89

WORK UNIT # 1653-88

DETAIL SUMMARY SHEET

TITLE: Limitations of Screening Tests in the Detection of von Willebrand's Disease

KEYWORDS: Von Willebrand's Disease, screening

PRINCIPAL INVESTIGATOR: Perry, James MAJ MC

ASSOCIATES: Alving, Barbara LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Hematology-Oncology Service

STATUS: Completed

APPROVAL DATE: Apr 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

Determine frequency of normal/abnormal screening tests in patients (50) determined by more sensitive tests to have Von Willebrand's Disease, all of whom were evaluated for excessive bleeding.

TECHNICAL APPROACH

Review of coagulation lab (WRAIR) records and Hematology-Oncology Clinic records where necessary. (Retrospective Review). Tabulation of frequency of clinical parameters (sites of bleeding, systems need for blood product transfusions, etc) and frequency of normal/abnormal screening comparisons to literature reviews on the topic.

PRIOR AND CURRENT PROGRESS

Fifty patients - found high frequency (less than 50%) of normal PTT, bleeding time, VIII-C in patients diagnosed to have VWD by low VWF-RG or ristocetin cofactor assay. Review completed

CONCLUSIONS

PTT and bleeding time inadequate as screening tests for VWD, since this is major diagnostic differential in patients presenting with abnormal bleeding. VWF:RG (or ristocetin cofactory assay) should be performed even if PTT/bleeding time is normal.

REPORT DATE: 05/08/89

WORK UNIT # 1654-88

DETAIL SUMMARY SHEET

TITLE: The Correlation Between Lupus Anticoagulants and Antibodies to Cardiolipin

KEYWORDS: lupus anticoagulants, cardiolipin antibodies

PRINCIPAL INVESTIGATOR: Alving, Barbara LTC MC

DEPARTMENT: Department of Medicine

STATUS: Completed

SERVICE: Hematology-Oncology Service

APPROVAL DATE: May 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

a) to determine in general medical patients with a prolonged APTT and lupus anticoagulant, the percent with anticardiolipin antibodies; b) to quantify levels of IgM and IgG anticardiolipin antibodies; c) to correlate levels of anticardiolipin antibodies with thrombotic events.

TECHNICAL APPROACH

Plasmas studied were those referred to WRAIR Coag Lab evaluation of unexplained prolongation of the APTT. The lupus anticoagulant was measured in a coagulation assay developed in our lab and published in Thrombosis Haemostasis in 1985. A solid phase ELISA was used for measurement of anticardiolipin antibodies.

PRIOR AND CURRENT PROGRESS

A paper has been submitted to the American Journal of Medicine. Plasmas from forty-seven patients were studied. The protocol is closed. This was a retrospective study of plasmas.

CONCLUSIONS

There is excellent correlation between a lupus anticoagulant and a positive assay for anticardiolipin antibody. Patients with high levels of anticardiolipin antibody are at-risk for thrombosis.

REPORT DATE: 01/09/90

WORK UNIT # 1655-88

DETAIL SUMMARY SHEET

TITLE: Retroviral Mediated Genetic Transfer of Radiation Resistance to  
Ataxia-Telangiectasia Cell Lines

KEYWORDS:

PRINCIPAL INVESTIGATOR: Giguere, Jeffrey MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Hematology-Oncology Service

STATUS: Terminated  
APPROVAL DATE: May 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

ADMINISTRATIVELY TERMINATED

TECHNICAL APPROACH

ADMINISTRATIVELY TERMINATED

PRIOR AND CURRENT PROGRESS

ADMINISTRATIVELY TERMINATED

CONCLUSIONS

ADMINISTRATIVELY TERMINATED

REPORT DATE: 03/16/89

WORK UNIT # 1656-88

DETAIL SUMMARY SHEET

TITLE: Magnetic Resonance Imaging in the Staging and Evaluation of Response to Therapy in Small Cell Carcinoma of the Lung

KEYWORDS:

PRINCIPAL INVESTIGATOR: Redmond, John COL MC

DEPARTMENT: Department of Medicine  
SERVICE: Hematology-Oncology Service

STATUS: Ongoing  
APPROVAL DATE: May 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

Fifty patients with SCLC, to determine the value of MR imaging in initial staging to detect metastatic disease in the following sites: adrenal, brain, etc.

TECHNICAL APPROACH

Conventional staging modalities are compared to MR imaging at the time of initial staging and after induction therapy.

PRIOR AND CURRENT PROGRESS

Nine patients entered. No adverse reactions. No withdrawals. Additional disease (to conventional staging) has been identified in two patients which changed treatment.

CONCLUSIONS

No findings yet.

REPORT DATE: 05/18/89

WORK UNIT # 1657-88

DETAIL SUMMARY SHEET

TITLE: Long Term 5-FU Infusion for Recurrent Head and Neck Cancer, A Phase II Pilot Study

KEYWORDS: 5-fluorouracil, cancer, continuous infusion

PRINCIPAL INVESTIGATOR: Ward, Frank MAJ MC

ASSOCIATES: Lombardo, Frederick MAJ MC; Cobb, Patrick CPT MC

DEPARTMENT: Department of Medicine  
SERVICE: Hematology-Oncology Service

STATUS: Ongoing  
APPROVAL DATE: Jun 1988

FUNDING: Current FY: \$13,650 Previous FYs: \$ 0 Total: \$ 13,650

STUDY OBJECTIVE

a) Assess effectiveness of a continuous infusion of 5-FU in patients with recurrent head and neck cancer; b) Assess the toxicity of a continuous infusion of 5-FU in patients with recurrent head and neck cancer.

TECHNICAL APPROACH

All adult patients with recurrent head and neck cancer who meet the eligibility requirements and consent to the protocol will have central venous catheter placed (if one is not already in place) and will be subsequently treated with 24 hour per day continuous infusion 5-FU at 300 mg/m<sup>2</sup>/day dose along with oral vitamin B6 to reduce the skin toxicity of the drug (in regard to hand-foot reaction). The drug will be continued in the absence of tumor progression or serious toxicity.

PRIOR AND CURRENT PROGRESS

Limited funding prevented patient accrual since the study could not begin until portable pumps could be bought. The funding for these pumps was obtained in early 1989 and the pumps were received in late February, 1989. The first patient was put on study in early May, 1989. The interval between obtaining the pumps and beginning patient accrual involved time needed to educate the various services (Oncology, Otolaryngology, General Surgery) of the availability of the protocol for patient accrual. No serious or unexpected adverse reactions to date. It is too early to assess for any benefit. Total patients on study: 1.

CONCLUSIONS

No conclusions can be made at this time. Patient accrual will continue.

REPORT DATE: 01/10/90

WORK UNIT # 1658-88

DETAIL SUMMARY SHEET

TITLE: Verification of the Heterogeneity of Lupus Anticoagulant Using Purified IgG and IgM from Patients with Lupus Anticoagulant

KEYWORDS: lupus anticoagulant, cardiolipin antibodies

PRINCIPAL INVESTIGATOR: Alving, Barbara LTC MC

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Hematology-Oncology Service

APPROVAL DATE: Jul 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To obtain blood from patients who have a lupus anticoagulant for the purpose of purifying and characterizing the antiphospholipid activity as being in the IgG or IgM fraction.

TECHNICAL APPROACH

IgG and IgM will be purified by column chromatography using DEAE cellulose from patient plasma.

PRIOR AND CURRENT PROGRESS

Plasmas from eight patients have been obtained and the immunoglobulins have been purified. They have been studied in both a clotting assay to determine their lupus anticoagulant activity and in a solid-phase ELISA using cardiolipin as the phospholipid source.

CONCLUSIONS

Most lupus anticoagulants are present as IgG and IgM antiphospholipid activity in a given patient's plasma.

REPORT DATE: 01/10/90

WORK UNIT # 1659-88

DETAIL SUMMARY SHEET

TITLE: Antisickling Effect of Erythrocyte 2,3-DPG Depletion

KEYWORDS: sickle cell, 2,3-DPG, hemoglobin S

PRINCIPAL INVESTIGATOR: Kark, John COL MC

ASSOCIATES: Poillon, William PhD; Hicks, Cecil

DEPARTMENT: Department of Medicine  
SERVICE: Hematology-Oncology Service

STATUS: Ongoing

APPROVAL DATE: Aug 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

a) To evaluate the extent of the antisickling effect produced by in vitro depletion of erythrocyte 2,3-DPG (2,3-diphosphoglycerate) in red cells from patients with sickle cell disease; b) to measure the contributions made by each of several mechanisms for this effect; c) to define optimum conditions for minimal levels of enzyme activators to achieve this effect.

TECHNICAL APPROACH

Small amounts of whole blood (30 ml) are drawn from patients with sickle cell disease or trait, the cells are washed, resuspended with activators of red cell 2,3-DPG phosphatase activity (phosphoglycolate or metabisulfite) or in control media, incubated for several hours, washed, resuspended in buffer and equilibrated with varying levels of po<sub>2</sub>, and fixed. The percentage of sickled cells are compared for treated versus control samples. Oxygen affinity, 2,3-DPG, ATP, pH, and drug levels are measured in both types of cells.

PRIOR AND CURRENT PROGRESS

Studies on samples from 14 subjects demonstrate: 1) maximal depletion of 2,3-DPG reduced sickling to < 50% of control levels throughout the physiologic range of po<sub>2</sub>; 2) A clear dose-response exists with more reduction in sickling for greater depletion of 2,3-DPG; 3) oxygen-dependent and oxygen independent mechanisms were measured, and 4) drug levels were at least 100-fold lower than for hemoglobin modifying agents. Both treatments resulted in metabolically viable cells with little change in ATP or glycolysis.

CONCLUSIONS

We have demonstrated that 2,3-DPG is a more substantial factor in pathogenesis of disease from sickling than previously recognized. Because enzyme activators are active at uM levels, this implies a novel therapeutic approach to sickling disorders which avoids the high concentrations limiting hemoglobin modifying agents.

REPORT DATE: 06/27/89

WORK UNIT # 1682-80

DETAIL SUMMARY SHEET

TITLE: WRAMC 7910 Group C Drugs for Use as Single Agents in the Treatment of Various Neoplastic Diseases

KEYWORDS: neoplastic, leukemia, 5-azacytidine

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine

STATUS: Completed

SERVICE: Hematology-Oncology Service

APPROVAL DATE: Oct 1979

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine the efficacy of 5-azacytidine in the treatment of acute granulocytic leukemia in patients previously refractory to other active antileukemic drugs.

TECHNICAL APPROACH

Non-randomized study in which all eligible patients receive 150-200 mg/m<sup>2</sup> x 5 IV every 14 to 21 days depending upon recovery from myelosuppression and bone marrow findings.

PRIOR AND CURRENT PROGRESS

Study has been open at WRAMC since 10-79. During the past 10 years only two patients were entered. Both patients expired with disease, having had minimal response to this drug.

CONCLUSIONS

Data too sparse. Two of two patients showed minimal response.

REPORT DATE: 01/12/90

WORK UNIT # 9021-82

DETAIL SUMMARY SHEET

TITLE: Anion Permeability of Sickle Cell Trait Red Cells

KEYWORDS: erythrocyte, hemoglobins, anion

PRINCIPAL INVESTIGATOR: Kark, John LTC MC

DEPARTMENT: Department of Medicine

STATUS: Completed

SERVICE: Hematology-Oncology Service

APPROVAL DATE: Feb 1982

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine whether anion permeability of erythoryctes (RBC) is related to binding of abnormal hemoglobins, including hemoglobin S (Hb S) to the membrane by testing whether Cl<sup>-</sup> permeability is increased in cells containing Hb S and by determining whether repeated sickling alters the Cl<sup>-</sup> permeability of cells which contain Hb S.

TECHNICAL APPROACH

Erythrocytes from volunteers with Hb AA, Hb SS, or Hb AS were examined for Cl<sup>-</sup> permeability and no difference was found at a non-physiologic pH, chosen because of the stability of Cl<sup>-</sup> flux at high pH. Studies are planned using a physiologic pH to examine the same parameters.

PRIOR AND CURRENT PROGRESS

Studies on red cells from volunteers with Hb AA, Hb AS, and Hb SS demonstrated no difference in Cl<sup>-</sup> efflux. This observation has become more significant since recent work has demonstrated alteration of Band 3 protein by precipitated hemoglobin S. Negative results would therefore be of considerable interest, establishing that the Cl<sup>-</sup>-transporter was still able to function despite modification.

CONCLUSIONS

Our data suggests that, despite modification of Band 3 by hemoglobin S, the anion transporter functions normally in the S hemoglobinopathies.

REPORT DATE: 10/17/88

WORK UNIT # 9022-83

DETAIL SUMMARY SHEET

TITLE: Studies of the Proliferation and Differentiation of Pluripotent Stem Cells and Committed Hematopoietic Precursors from Normal Bone Marrow Maintained in Continuous Long-term Cultures

KEYWORDS: stem cells, differentiation

PRINCIPAL INVESTIGATOR: La Russa, Vincent PhD

ASSOCIATES: Salvado, August COL MC; Knight, Robert LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Hematology-Oncology Service

STATUS: Ongoing

APPROVAL DATE: Oct 1982

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To define mechanisms by which progenitor cells in the bone marrow replicate themselves and go on to form mature blood cells.

TECHNICAL APPROACH

The methods involved are 1) The use of culture tubes and a defined media to study the behavior of stem cells for period up to 8 weeks in culture, and 2) The use of clonal assays to quantitate the number of stem cells grown in culture.

PRIOR AND CURRENT PROGRESS

We have developed a unique quantitative system to examine the effects of hematopoietic regulators over a period of 6-8 weeks. They include cytokines as well as accessory cell function in the hematopoietic microenvironment.

CONCLUSIONS

The findings of these studies will ultimately result in the development of ideal conditions in culture flasks which may allow for extensive replication of progenitor cells. These cells may then be used in clinical situations in which a deficiency in mature or immature blood cells are needed.

REPORT DATE: 01/30/90

WORK UNIT # 9903

DETAIL SUMMARY SHEET

TITLE: In Vitro Induction of Terminal Differentiation in Oral-Pharyngeal  
Leukoplakia with Gammer Interferon and Tumor Necrosis Factor

KEYWORDS:

PRINCIPAL INVESTIGATOR: Dunning, David MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Hematology-Oncology Service

STATUS: Terminated  
APPROVAL DATE: Aug 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

ADMINISTRATIVELY TERMINATED.

TECHNICAL APPROACH

ADMINISTRATIVELY TERMINATED.

PRIOR AND CURRENT PROGRESS

ADMINISTRATIVELY TERMINATED.

CONCLUSIONS

ADMINISTRATIVELY TERMINATED.

REPORT DATE: 10/30/89

WORK UNIT # 1929

DETAIL SUMMARY SHEET

TITLE: Oropharyngeal Colonization of Neonates with Gram-negative Bacilli

KEYWORDS: oropharyngeal, neonate, colonization

PRINCIPAL INVESTIGATOR: Cross, Alan LTC MC

ASSOCIATES: Weisman, Leonard LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Infectious Disease Service

STATUS: Terminated  
APPROVAL DATE: Nov 1983

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine if oropharyngeal cells of the neonate have cell-surface fibronectin and if so does this affect the adherence of gram-negative flora.

TECHNICAL APPROACH

Healthy, term newborn infants, born at WRAMC, who did not receive antibiotics, who will be followed at WRAMC, were entered after parental consent. Oropharyngeal swabs done at birth, 3 days, 2 weeks, and 2, 4, and 6 months were obtained from buccal epithelial cells. Those samples were then analyzed for cell surface fibronectin and bacterial adherence.

PRIOR AND CURRENT PROGRESS

ADMINISTRATIVELY TERMINATED.

CONCLUSIONS

ADMINISTRATIVELY TERMINATED.

REPORT DATE: 05/24/89

WORK UNIT # 1933

DETAIL SUMMARY SHEET

TITLE: Characterization of Leptospiral Toxins

KEYWORDS: leptospiral, toxin

PRINCIPAL INVESTIGATOR: McClain, Bruce LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Infectious Disease Service

STATUS: Completed  
APPROVAL DATE: Apr 1984

FUNDING: Current FY: \$ 489 Previous FYs: \$ 12,347 Total: \$ 12,836

STUDY OBJECTIVE

To characterize Leptospiral toxins and virulence factors.

TECHNICAL APPROACH

To develop a virulent strain of leptospira, we developed a bioassay using the same animal that exhibits toxicity so that we can measure sublethal injury. We planned to use urinary Beta-2-Microglobuli excretion. We then needed to look at the toxicity of various fractions of the leptospiral culture medium to see if there is any cytotoxicity in an invitro model. We then plan to use those same fractions in the animal model.

PRIOR AND CURRENT PROGRESS

We have confirmed resistance as a virulence factor and studied the mechanism of serum resistance and published our preliminary results in and Abstract at the 1988 ASM Meeting. We have collected and looked at 16 human strain for antibiotic resistance and published our results in an abstract at the 1988 ICAAC. Manuscripts are now in preparation. Since the departure of Dr. Joshi and the availability of laboratory space at WRAIR I would like to terminate the protocol at WRAMC althoug I will be continuing the study at WRAIR.

CONCLUSIONS

1) Complement resistance is a virulence factor but it is not responsible for lethality only infection. 2) Mechanism of complement resistance is not due to dialic acid on the surface or organism. 3) Virulent human organisms are not antibiotic resistant.

REPORT DATE: 05/29/87

WORK UNIT # 1937

DETAIL SUMMARY SHEET

TITLE: Development of Human Monoclonal Antibodies from Peripheral Blood Lymphocytes

KEYWORDS: monoclonal antibody, microbial pathogens, human

PRINCIPAL INVESTIGATOR: Sadoff, Jerald COL MC

DEPARTMENT: Department of Medicine  
SERVICE: Infectious Disease Service

STATUS: Terminated  
APPROVAL DATE: Oct 1984

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To produce human monoclonal antibodies against medically important bacteria, virus, and fungi.

TECHNICAL APPROACH

Fuse human peripheral blood cells to myeloma fusion partners. Peripheral blood to be taken from patients colonized with pathogens or in early recovery phase of infections.

PRIOR AND CURRENT PROGRESS

ADMINISTRATIVELY TERMINATED

CONCLUSIONS

ADMINISTRATIVELY TERMINATED

REPORT DATE: 06/07/89

WORK UNIT # 1940

DETAIL SUMMARY SHEET

TITLE: Mediators of Cell Immunity in Patients Infected with Intracellular Microorganisms

KEYWORDS: leishmania, macrophages, lymphokines

PRINCIPAL INVESTIGATOR: Hoover, David LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Infectious Disease Service

STATUS: Ongoing  
APPROVAL DATE: Jul 1985

FUNDING: Current FY: \$ 8,473 Previous FYs: \$ 0 Total: \$ 8,473

STUDY OBJECTIVE

Develop a serologic assay for non-interferon macrophage activation factors in human blood.

TECHNICAL APPROACH

Serum from infected patients is examined at various times in the course of disease for monocyte activation activity. Activity is induction of a leishmanicidal state in human monocytes. The long-term goal is to establish an assay that will not require use of other human cells as an indicator system.

PRIOR AND CURRENT PROGRESS

We have previously described a lymphokine that induces leishmanicidal activity in human monocytes cultured in vitro and shown its secretion by a human T cell line. We also have examined production of IL-1 by human monocytes in response to activation factors. We found that interferon- $\gamma$  cooperates with endotoxin to induce IL-1 production, but has little, if any, effect on production of IL-1 by monocytes cultured with amphotericin B.

CONCLUSIONS

Amphotericin B induces IL-1 production by human monocytes faster than endotoxin, and does not show synergistic interaction with interferon- $\gamma$ . This suggests an alternative mechanism for macrophage stimulation by amphotericin B.

REPORT DATE: 12/28/88

WORK UNIT # 1942

DETAIL SUMMARY SHEET

TITLE: Rat Tissue Affinities of Leptospirae

KEYWORDS: leptospirosis, leptospira interrogans, toxin

PRINCIPAL INVESTIGATOR: McClain, Bruce LTC MC

DEPARTMENT: Department of Medicine

STATUS: Completed

SERVICE: Infectious Disease Service

APPROVAL DATE: Feb 1986

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine if different tissues have different affinities for radiolabeled L. Interrogans.

TECHNICAL APPROACH

Measure relative binding of radiolabeled germs to various rat tissue fractions.

PRIOR AND CURRENT PROGRESS

Due to additional new duties at WRAIR the PI has been and will be unable to complete the protocol. It has had no charges on it in the last year.

CONCLUSIONS

Study completed.

REPORT DATE: 06/01/89

WORK UNIT # 1949

DETAIL SUMMARY SHEET

TITLE: Passage of L. donovani Amastigotes in Syrian Golden Hamsters

KEYWORDS: leishmania, Syrian hamsters

PRINCIPAL INVESTIGATOR: Hoover, David LTC MC

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Infectious Disease Service

APPROVAL DATE: Dec 1986

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

Provide amastigotes for use in in vitro studies on activation of human monocytes.

TECHNICAL APPROACH

Amastigotes are harvested from spleens of infected hamsters. Parasites are released from spleen cells by grinding in a tissue grider and purified by centrifugation. They are then used for in vitro studies or injected into other hamsters to continue the passage.

PRIOR AND CURRENT PROGRESS

We have harvested amastigotes from hamsters until 9/88; we have temporarily stopped using the animals while we concentrated on other assays of monocyte activation.

CONCLUSIONS

This technique has proven satisfactory as a source of amastigotes for our in vitro assays.

REPORT DATE: 05/19/89

WORK UNIT # 1956

DETAIL SUMMARY SHEET

TITLE: Neutrophil Function in Patients with Diabetes Mellitus

KEYWORDS: diabetes mellitus, neutrophil

PRINCIPAL INVESTIGATOR: Cross, Alan COL MC

ASSOCIATES: Glass, Allan COL MC; Duncan, William MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Infectious Disease Service

STATUS: Ongoing  
APPROVAL DATE: Jun 1987

FUNDING: Current FY: \$ 1,680 Previous FYs: \$ 5,556 Total: \$ 7,236

STUDY OBJECTIVE

To assess the neutrophil function of patients with diabetes mellitus and to determine if impaired functional responses of diabetic neutrophils are related to a defect in the incorporation of exogenous inositol into hormonally sensitive phosphatidyl inositol pools. To assess lymphocyte function in diabetics by measuring expression of IL2 receptors, HLA-DR antigens and IL2 production. To assess neutrophil function by measuring calcium levels, membrane depolarization.

TECHNICAL APPROACH

Since submitting our amendment to the protocol we have studied 27 patients and 20 control subjects. The most significant finding has been that the initial rates of superoxide formation in diabetics is twice that of controls; however, 10 min after stimulation the neutrophils of diabetic patients generate levels of superoxide that are 25% that of controls. Resting, but not stimulated, intracellular calcium levels also differed between the two groups. The expression of IL2 receptors in response to some stimuli differed between the two groups. We are not correlating these differences with clinical parameters.

PRIOR AND CURRENT PROGRESS

Since submitting our amendment to the protocol we have studied 27 patients and 20 control subjects. The most significant finding has been that the initial rates of superoxide formation in diabetics is twice that of controls; however, 10 min after stimulation the neutrophils of diabetic patients generate levels of superoxide that are 25% that of controls. Resting, but not stimulated, intracellular calcium levels also differed between the two groups. The expression of IL2 receptors in response to some stimuli differed between the two groups. We are not correlating these differences with clinical parameters.

CONCLUSIONS

It appears that there are significant differences in neutrophil and perhaps mononuclear cell function in diabetic patients; however, more patients with type I diabetes and with different levels of control are required before we can correlate these laboratory findings with clinical state.

REPORT DATE: 01/21/90

WORK UNIT # 1959

DETAIL SUMMARY SHEET

TITLE: Treatment of Systemic Fungal Infections with Itraconazole

KEYWORDS:

PRINCIPAL INVESTIGATOR: Chulay, Jeffrey COL MC

DEPARTMENT: Department of Medicine  
SERVICE: Infectious Disease Service

STATUS: Terminated  
APPROVAL DATE: Jul 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

ADMINISTRATIVELY TERMINATED.

TECHNICAL APPROACH

ADMINISTRATIVELY TERMINATED.

PRIOR AND CURRENT PROGRESS

ADMINISTRATIVELY TERMINATED.

CONCLUSIONS

ADMINISTRATIVELY TERMINATED.

REPORT DATE: 08/21/89

WORK UNIT # 1962

DETAIL SUMMARY SHEET

TITLE: Gonorrhea Infection in the Male: Semiquantitation of the Infectious Inoculum

KEYWORDS: gonorrhea, urethritis, semen

PRINCIPAL INVESTIGATOR: Johnson, Steven CPT MC

ASSOCIATES: Hicks, Charles; Soprey, Pandu; Tramont, Edmund

DEPARTMENT: Department of Medicine  
SERVICE: Infectious Disease Service

STATUS: Ongoing  
APPROVAL DATE: Sep 1988

FUNDING: Current FY: \$ 0 Previous FY: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To study colony counts and colony antigenic variations among gonorrhea isolates from the sperm of patients with acute gonococcal urethritis.

TECHNICAL APPROACH

Samples obtained from the patient are diluted and plated onto agar. Colony counts per milliter of sperm are calculated. Isolates are further studied using gel electrophoresis and immunoblot techniques.

PRIOR AND CURRENT PROGRESS

At this time, we have only been able to enroll three patients. We believe this is mostly due to the time constraints of the protocol (we can only enroll patients between 0700 and 1500) and a continued lack of awareness among other services about this protocol.

CONCLUSIONS

Patient enrollment has been quite slow; however, we remain committed to increasing awareness of the protocol. Each patient enrolled provides a great deal of information and we believe we can reach important conclusions with a limited number of patients.

REPORT DATE: 05/31/89

WORK UNIT # 9103

DETAIL SUMMARY SHEET

TITLE: Monoclonal Antibodies to N. Gonorrhoeae

KEYWORDS: monoclonal antibody, N. Gonorrhoeae

PRINCIPAL INVESTIGATOR: Boslego, John LTC MC

ASSOCIATES: Soprey, Pandu PhD; Deal, Carolyn PhD

DEPARTMENT: Department of Medicine  
SERVICE: Infectious Disease Service

STATUS: Ongoing  
APPROVAL DATE: Jul 1982

FUNDING: Current FY: \$ 1,359      Previous FYs: \$ 853      Total: \$ 2,212

STUDY OBJECTIVE

a) Develop monoclonal antibodies against cell wall antigens of Neisseria gonorrhoeae; b) Determine the functional characteristics of these monoclonal antibodies.

TECHNICAL APPROACH

Monoclonal antibodies are produced following immunization of mice and fusion of mouse spleen cells with mouse myeloma cells. Hybridoma cells are then screened for the production of monoclonal antibodies with specificity for surface antigen of N. Gonorrhoeae in an ELISA assay.

PRIOR AND CURRENT PROGRESS

Monoclonal antibodies with specificity for pilin protein have been tested against purified pili and N. Gonorrhoeae organisms in Western Blot assays. Type specific and cross-reactive monoclonal antibodies have been identified. These antibodies are currently being tested for reactivity to overlapping synthetic peptides designed from the pilin sequence in order to map the specific epitope of reactivity.

CONCLUSIONS

Surface-expressed pilin epitopes are potential gonococcal vaccine candidates. Identification of these epitopes with monoclonal antibodies is an important step in their development as vaccines.

REPORT DATE: 05/17/89

WORK UNIT # 1152

DETAIL SUMMARY SHEET

TITLE: In Vitro Analysis of Removal of Radiocontrast Agents (RCA) by Artificial Membranes

KEYWORDS: dialysis, radiocontrast, transport

PRINCIPAL INVESTIGATOR: Gouge, Steven MAJ MC

ASSOCIATES: Moore, Hirszel

DEPARTMENT: Department of Medicine  
SERVICE: Nephrology Service

STATUS: Ongoing  
APPROVAL DATE: Jun 1987

FUNDING: Current FY: \$ 1,332 Previous FYs: \$ 0 Total: \$ 1,332

STUDY OBJECTIVE

1) To study removal of radiocontrast agents (RCA) by three types of artificial membranes. 2) To determine performance curves depicting clearance as a function of operating parameters to assist in assessing optimal conditions for RCA removal.

TECHNICAL APPROACH

We used an in vitro system consisting of standard dialysis machines and solutions. We made test perfusates by adding urea and one of 2 RCA to normal saline. We ran these solutions through three types of dialyzers to different flow and pressures to assess RCA clearance.

PRIOR AND CURRENT PROGRESS

RCA mass transport was measured with Cuprophan (CU) and Polyacrilonitrile (PA) dialyzers. Both Hexabrix and Renografin RCA were used. Clearance of Renografin exceeded clearance of Hexabrix in both types of dialyzers, and is attributed to lower molecular weight of the former. Clearance of both RCA was affected by TMP in only PA dialyzers, and is due to convective transport. Diffusive transport accounted for RCA removal in Cuprophan dialyzers. PA dialyzers are best for removal of RCA.

CONCLUSIONS

Demonstration of optimum operational characteristics will allow us to embark on a prospective study in patients at high risk for RCA toxicity.

REPORT DATE: 08/07/89

WORK UNIT # 1154

DETAIL SUMMARY SHEET

TITLE: The Relationship Between the Degree of Anemia and the Degree of Chronic Renal Failure

KEYWORDS: anemia, azotemia, renal failure

PRINCIPAL INVESTIGATOR: Howard, Andrew MAJ MC

ASSOCIATES: Welch, Paul CPT; Moore, Jack LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Nephrology Service

STATUS: Completed

APPROVAL DATE: Sep 1987

FUNDING: Current FY: \$ 206 Previous FYs: \$ 0 Total: \$ 206

STUDY OBJECTIVE

To establish a method for determining the expected degree of anemia for a given level of renal failure.

TECHNICAL APPROACH

Retrospective chart review of all patients seen in Nephrology Clinic for one year. Patients with comorbid disorders known to affect red cells were excluded. Hemoglobin concentration was plotted as a function of three indices of renal failure, and confidence intervals were calculated.

PRIOR AND CURRENT PROGRESS

One hundred fifty-seven charts were reviewed. Final study cohort was 106. Hematocrit varies 10 vol % at any given level of renal function. Thus, the degree of anemia varies widely and precludes assigning renal failure as a cause of anemia with confidence.

CONCLUSIONS

This study was published in the American Journal of Medical Science and is completed.

REPORT DATE: 08/07/89

WORK UNIT # 1155

DETAIL SUMMARY SHEET

TITLE: The Effect of Thyroid Hormone Administration in Acute Renal Failure

KEYWORDS: renal failure, thyroxine, dialysis

PRINCIPAL INVESTIGATOR: Moore, Jack LTC MC

ASSOCIATES: Johnson, J. COL MC; Burman, Kenneth Col MC

DEPARTMENT: Department of Medicine  
SERVICE: Nephrology Service

STATUS: Ongoing  
APPROVAL DATE: Sep 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine whether patients with acute renal failure (ARF) have improved survival when treated with thyroxine compared to patients who do not receive T4; to determine whether T4 alters the severity of ARF; to assess the thyroid axis in patients with ARF; and to determine whether T4 affects severity and mortality of ARF in parallel, or are these effects disparate.

TECHNICAL APPROACH

Adults with RF are stratified into two groups based on entry serum creatinine and urine output. They then receive either T4 or placebo in a double blind, placebo controlled study. Thyroid hormones are measured at intervals, and renal function is assessed. Data are analyzed in context with survival variables, thyroid function parameters, and dialysis requirements.

PRIOR AND CURRENT PROGRESS

Seventeen patients/family members were approached for recruitment into this study since September, 1988. So far we have been unsuccessful, as patient's family members have appeared to be unwilling to provide informed consent. We have developed a "standardized" approach to these patients and hope to meet with more success in recruitment.

CONCLUSIONS

No conclusions can be drawn; recruitment efforts continue.

REPORT DATE: 10/17/88

WORK UNIT # 1156

DETAIL SUMMARY SHEET

TITLE: Retrospective Analysis of the Use of Renal Ultrasound at Walter Reed Army Medical Center

KEYWORDS: ultrasound, kidney, obstruction

PRINCIPAL INVESTIGATOR: Gouge, Steven MAJ MC

ASSOCIATES: Lee, Robert MAJ MC; Howard, Andrew MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Nephrology Service

STATUS: Ongoing  
APPROVAL DATE: Oct 1987

FUNDING: Current FY: \$ 1,131      Previous FYs: \$ 0      Total: \$ 1,131

STUDY OBJECTIVE

a) To survey the application of diagnostic ultrasonography at WRAMC by all requesting physicians; b) To classify as standard or non-standard the indications for performing the sonogram; c) to determine the relative frequency of abnormal versus normal results based on this distinction.

TECHNICAL APPROACH

All ultrasound reports in six-month increments are collated and the appropriate records are reviewed. Information from the records are then categorized into a) the indication for the ultrasound, b) the type of requesting physician, and c) the result of the ultrasound. A and C are subclassified into different strata which assist in data analysis. Data are then analyzed in a matrix format.

PRIOR AND CURRENT PROGRESS

So far 101 charts have been analyzed. Seventy percent of the studies have been abnormal, with hydronephrosis and cysts being the most common abnormalities. Fiftysix percent of the studies were done for standard indications, while 44% were performed for non-standard indications. Nephrologists order ultrasounds in azotemic patients, while urologists order ultrasound to follow-up abnormalities on IVP.

CONCLUSIONS

No conclusions can be reached. Data collection and analysis is continuing.

REPORT DATE: 12/13/89

WORK UNIT # 1702

DETAIL SUMMARY SHEET

TITLE: Ventilatory Response to Carbon Dioxide in Presenile Dementia

KEYWORDS: dementia, control

PRINCIPAL INVESTIGATOR: Rajagopal, Krishnan LTC MC

ASSOCIATES: Derderian, Sarkis LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Pulmonary Disease Service

STATUS: Completed  
APPROVAL DATE: Jul 1980

FUNDING: Current FY: \$ 200 Previous FYs: \$ 1,466 Total: \$ 1,666

STUDY OBJECTIVE

To study load compensating mechanisms in patients with dementia.

TECHNICAL APPROACH

Ventilatory and loading responses to hypercapnia.

PRIOR AND CURRENT PROGRESS

Study completed in patients and submitted for publication.

CONCLUSIONS

Patients with dementia have impaired load compensating mechanisms suggesting an important role for the cerebral cortex in the normal regulation of respiration.

REPORT DATE: 01/25/90

WORK UNIT # 1705

DETAIL SUMMARY SHEET

TITLE: Determinants of Resistive-Loaded Breathing Response

KEYWORDS: respiratory drive, exercise, loaded breathing

PRINCIPAL INVESTIGATOR: Abbrecht, Peter PhD

ASSOCIATES: Rajagopal, Krishnan LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Pulmonary Disease Service

STATUS: Terminated

APPROVAL DATE: Sep 1980

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To determine the effects of inspiratory flow-resistive loading upon respiratory drive, the work of breathing, and chest and abdominal wall mechanics during exercise.

TECHNICAL APPROACH

To measure end-tidal PCO<sub>2</sub>, ventilation, esophageal and mouth occlusion pressures, and chest wall and abdominal wall excursion in normal subjects exercising at 30% VO<sub>2</sub> max while breathing through different inspiratory resistors.

PRIOR AND CURRENT PROGRESS

ADMINISTRATIVELY TERMINATED.

CONCLUSIONS

ADMINISTRATIVELY TERMINATED.

REPORT DATE: 01/02/90

WORK UNIT # 1707

DETAIL SUMMARY SHEET

TITLE: Relationship Between Respiratory Control Mechanisms and Nocturnal Desaturation in Diffuse Pulmonary Fibrosis

KEYWORDS: fibrosis, sleep, respiratory control

PRINCIPAL INVESTIGATOR: Rajagopal, Krishnan LTC MC

ASSOCIATES: Tenholder, Michael COL MC; Derderian, Sarkis LTC

DEPARTMENT: Department of Medicine  
SERVICE: Pulmonary Disease Service

STATUS: Ongoing  
APPROVAL DATE: Feb 1981

FUNDING: Current FY: \$ 1,309 Previous FYs: \$ 0 Total: \$ 1,309

STUDY OBJECTIVE

To examine the relationship between respiratory control mechanisms and sleep desaturation in patients with pulmonary fibrosis.

TECHNICAL APPROACH

Patients with well defined diffused pulmonary fibrosis will be included in the study and their results will be compared to results from similar tests performed in a group of volunteer controls. Nocturnal polysomnography and hypercapnic ventilatory and occlusion pressure (P100) responses will be performed to quantitate respiratory control mechanisms and nocturnal desaturation. The SPSS statistical package will be used for evaluation of correlates and cocorrelates.

PRIOR AND CURRENT PROGRESS

Six patient have been studied in the past (until last year). However, because sleep scoring had to be manually performed, the scoring was limited to few parameters only. Over the last year an automated sleep staging system has become available and since then four studies have been completed.

CONCLUSIONS

Despite the long delay in the completion of this protocol, we believe that it must be maintained for an additional twelve months. Personnel for the conduct of the study have finally become available and the necessary new equipment is here. Because all the necessary ingredients are finally here, the protocol should be completed soon.

REPORT DATE: 01/02/90

WORK UNIT # 1708

DETAIL SUMMARY SHEET

TITLE: Respiratory Control Mechanisms in Platral Myoclonus

KEYWORDS: myoclonus

PRINCIPAL INVESTIGATOR: Rajagopal, Krishnan LTC MC  
ASSOCIATES: Jabbari, Bahman COL MC

DEPARTMENT: Department of Medicine  
SERVICE: Pulmonary Disease Service

STATUS: Completed  
APPROVAL DATE: Feb 1981

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To assess respiratory control mechanisms in palatal myoclonus and test the hypothesis that the ventilatory response to hypercapnia is depressed in central brain stem abnormalities.

TECHNICAL APPROACH

Ventilatory and occlusion pressure responses to hypercapnia and flow resistive loading will be studied in patients with palatal myoclonus.

PRIOR AND CURRENT PROGRESS

Four patients have been studied so far.

CONCLUSIONS

Isolated palatal myoclonus is an extremely uncommon disturbance. Because additional patients have not been identified, no new patients will be included. The data from the study will be analyzed and submitted for publication in the near future. Once that process has been completed the protocol will be terminated.

REPORT DATE: 01/22/90

WORK UNIT # 1710

DETAIL SUMMARY SHEET

TITLE: Relationship between Respiratory Control Mechanisms and Nocturnal Desaturation in Obese Subjects

KEYWORDS: obesity, desaturation, sleep

PRINCIPAL INVESTIGATOR: Tamamoteber, Warren MAJ MC

ASSOCIATES: Rajagopal, Krishnan LTC MC

DEPARTMENT: Department of Medicine

SERVICE: Pulmonary Disease Service

STATUS: Terminated

APPROVAL DATE: Mar 1981

FUNDING: Current FY: \$ 398 Previous FYs: \$ 0 Total: \$ 398

STUDY OBJECTIVE

To examine the relationship between respiratory control mechanisms and nocturnal desaturation in obese subjects.

TECHNICAL APPROACH

Nocturnal polysomnography will be used for the evaluation of sleep desaturation. Ventilation and occlusion pressure responses to hypercapnia will be used to assess respiratory control.

PRIOR AND CURRENT PROGRESS

To date the major problem has been the non-availability of a technician. The protocol still is of significant value, and completion would yield useful new information. A certified sleep technician must be made available.

CONCLUSIONS

ADMINISTRATIVELY TERMINATED.

REPORT DATE: 02/17/89

WORK UNIT # 1711

DETAIL SUMMARY SHEET

TITLE: Pulmonary Function in Psoriatic Arthritis

KEYWORDS: psoriatic arthritis, respiratory, pulmonary function

PRINCIPAL INVESTIGATOR: Derderian, Sarkis LTC MC

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Pulmonary Disease Service

APPROVAL DATE: Mar 1981

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To define the limits of lung function in patients with psoriatic arthritis by doing a complete pulmonary function evaluation in a group of subjects with this diagnosis.

TECHNICAL APPROACH

Lung function is being assessed by measuring air flow using spirometry, lung volumes by plethysmography and gas exchange with diffusing capacity.

PRIOR AND CURRENT PROGRESS

During the past year there was no progress because of difficulties recruiting patients. This problem has been discussed with dermatology and is hopefully resolved. One abstract has been presented and published. The paper was not accepted in part because of the lack of control group.

CONCLUSIONS

We have studied 18 subjects to date and have demonstrated that many of these subjects do have mild abnormalities in lung function.

REPORT DATE: 01/17/90

WORK UNIT # 1714

DETAIL SUMMARY SHEET

TITLE: Mechanisms Limiting Exercise Ventilation in Chronic Obstructive Lung Disease

KEYWORDS: exercise, ventilation, COPD

PRINCIPAL INVESTIGATOR: Dillard, Thomas MAJ MC

ASSOCIATES: Derderian, Sarkis LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Pulmonary Disease Service

STATUS: Ongoing  
APPROVAL DATE: Sep 1983

FUNDING: Current FY: \$ 50 Previous FYs: \$ 120 Total: \$ 170

STUDY OBJECTIVE

To determine factors that limit ventilation at maximum exercise in patients with Chronic Obstructive Lung Disease.

TECHNICAL APPROACH

Continuous physiologic measurements are made during graded resistance exercise on a bicycle ergometer with esophageal balloon in place for the measurement of pleural pressure to determine the work of breathing.

PRIOR AND CURRENT PROGRESS

During FY 89 we studied 3 patients under this protocol. Additional work documenting technical methods was accomplished. Three manuscripts are under development or are anticipated for FY 90 and FY 91.

CONCLUSIONS

Work continues with continuing need for financial support; amount of \$500 for equipment and \$500 for manuscript fees and reprints may be anticipated.

REPORT DATE: 01/02/90

WORK UNIT # 1716

DETAIL SUMMARY SHEET

TITLE: Nasal Continuous Positive Airway Pressure (CPAP) in Obstructive Sleep Apnea (OSA)

KEYWORDS: NCPAP, sleep apnea

PRINCIPAL INVESTIGATOR: Rajagopal, Krishnan LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Pulmonary Disease Service

STATUS: Completed  
APPROVAL DATE: Jul 1984

FUNDING: Current FY: \$ 2,985 Previous FYs: \$ 2,848 Total: \$ 5,833

STUDY OBJECTIVE

To examine the efficacy of nasal continuous positive airway pressure in the sleep apnea syndrome.

TECHNICAL APPROACH

Polysomnographic and respiratory control studies will be done prior to and during the administration of nasal continuous positive airway pressure.

PRIOR AND CURRENT PROGRESS

Fourteen patients have been studied. NCPAP produced significant improvement in sleep symptoms.

CONCLUSIONS

Nasal CPAP is an effective form of treatment for sleep apnea. Further work on this protocol will not be necessary.

REPORT DATE: 10/17/89

WORK UNIT # 1717

DETAIL SUMMARY SHEET

TITLE: Prediction of Maximum Exercise Response from Resting Pulmonary Function  
in Patients with Chronic Obstructive Pulmonary Disease

KEYWORDS: exercise, ventilation, COPD

PRINCIPAL INVESTIGATOR: Dillard, Thomas MAJ MC

DEPARTMENT: Department of Medicine  
SERVICE: Pulmonary Disease Service

STATUS: Ongoing  
APPROVAL DATE: May 1985

FUNDING: Current FY: \$ 215 Previous FYs: \$ 0 Total: \$ 215

STUDY OBJECTIVE

To test the hypothesis that assessment of inspiratory function in addition to expiratory function can improve the prediction of the exercise response of patients with chronic obstructive pulmonary disease.

TECHNICAL APPROACH

To evaluate parameters of both inspiratory and expiratory function in COPD patients and to perform exercise tests in this group. Using these variables prediction formulae with the highest  $r^2$  values will be identified for maximum exercise ventilation and oxygen consumption.

PRIOR AND CURRENT PROGRESS

Protocol remains active. Additional cases have been collected for analysis under this protocol. A total of 36 cases have been indentified thus far for inclusion. Development of prediction models has been initiated.

CONCLUSIONS

Continuing support is required.

REPORT DATE: 02/17/89

WORK UNIT # 1720

DETAIL SUMMARY SHEET

TITLE: Pilot Study On the Use of Conjunctival Oxygen Tension Monitoring in the Sleep Apnea Syndrome

KEYWORDS: oxygen, sleep apnea, conjunctival monitor

PRINCIPAL INVESTIGATOR: Derderian, Sarkis LTC MC

ASSOCIATES: Mohr, Lawrence LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Pulmonary Disease Service

STATUS: Ongoing

APPROVAL DATE: Apr 1987

FUNDING: Current FY: \$11,818 Previous FYs: \$ 1,649 Total: \$ 13,467

STUDY OBJECTIVE

To compare conjunctival oxygen tension monitoring with ear oximetry in Black sleep apneic patients.

TECHNICAL APPROACH

Using Polysomnography (PSG) we plan to compare the two devices. In that skin pigmentation affects oximetry the conjunctival monitor should be reliable index.

PRIOR AND CURRENT PROGRESS

Seven subjects have been evaluated thus far. Neither device (Cjo<sub>2</sub> monitor or pulse oximetric) measures oxygen directly and data have been difficult to interpret. An addendum has been submitted to now include direct arterial monitoring so that both devices can be compared to a single gold standard (direct arterial O<sub>2</sub> tension).

CONCLUSIONS

Data suggest that the Cjo<sub>2</sub> monitor is a safe alternative to the research but has not addressed whether it is superior to standard oximetry in this group of subjects.

REPORT DATE: 05/12/89

WORK UNIT # 1721

DETAIL SUMMARY SHEET

TITLE: Comparison of Prepregnancy and Postpartum Fitness Levels: A Pilot Study

KEYWORDS: fitness, pregnancy, activity

PRINCIPAL INVESTIGATOR: South-Paul, Jeanette MAJ MC

ASSOCIATES: Tenholder, Michael COL MC; Rajagopal, Krishnan LTC

DEPARTMENT: Department of Medicine  
SERVICE: Pulmonary Disease Service

STATUS: Ongoing  
APPROVAL DATE: Jun 1987

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To assess whether women regain their prepregnancy level of fitness within 30 days after delivery, following an uncomplicated pregnancy.

TECHNICAL APPROACH

Prepregnancy fitness will be assessed via 1) pulmonary function and cycle ergometer measurement of maximal oxygen consumption, 2) body fat determination via skin impedance and skin caliper methods, 3) baseline activity assessment via Minnesota Leisure Time Activity Questionnaire, and 4) psychiatric assessment via a child psychiatrist. The above steps will be completed prior to becoming pregnant and again thirty days following delivery.

PRIOR AND CURRENT PROGRESS

Sixteen women have been entered into the study since the project was begun. Six have become pregnant since entering the study, have delivered and have completed the requirements of the protocol. Five subjects have been entered in the study, have become pregnant, but have not yet delivered. Five subjects have had prepregnancy data collected but have not yet become pregnant. Preliminary evaluation of data on the first five subjects has been done. An abstract describing these results has been submitted to the American Academy of Family Physicians Annual Scientific Competition - scheduled for September, 1989. A copy of this abstract has been included with this report.

CONCLUSIONS

No final conclusions are yet available.

REPORT DATE: 05/30/89

WORK UNIT # 1722

DETAIL SUMMARY SHEET

TITLE: Flow-volume Loops and Routine Spirometry in Patients with Exercise-induced Asthma

KEYWORDS: exercise-induced asthma, flow-volume loops

PRINCIPAL INVESTIGATOR: Eliasson, Arn MAJ MC

ASSOCIATES: Rajagopal, Krishnan LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Pulmonary Disease Service

STATUS: Ongoing

APPROVAL DATE: Jul 1987

FUNDING: Current FY: \$00,000 Previous FYs: \$ 0 Total: \$ 100,000

STUDY OBJECTIVE

To study changes in inspiratory air flow in EIA patients by evaluating the inspiratory and expiratory limbs of the flow-volume loops during airways challenge testing.

TECHNICAL APPROACH

Patients referred for evaluation of possible EIA are given opportunity to enroll in the study which consists of four standardized airway challenge tests which the subject undergoes in randomized order. These consist of exercise challenge, methacholine inhalation, cold and dry gas hyperventilation. Immediately before and after the challenge and at five minute intervals subsequently, the patient performs a flow-volume loop maneuver to detect airway reactivity. The challenges are administered on different days, between the hours of 7 and 9 AM in order to standardize the diurnal variation.

PRIOR AND CURRENT PROGRESS

Forty subjects (20 patients had 20 controls) have been enrolled in the study. Thirty nine of the subjects have completed all four challenge tests in the series as outlined in the protocol. There remains one subject to complete one challenge test before all data are collected. This will be done before the end of May 1989. With the help of DCI's Dr. T. R. Young, data analysis is beginning.

CONCLUSIONS

Data analysis is ongoing. The techniques of airway challenge used in the protocol are safe and well tolerated.

REPORT DATE: 02/15/89

WORK UNIT # 1724

DETAIL SUMMARY SHEET

TITLE: Mechanisms of Hypoxia During Simulated Air Travel in Patients with Chronic Obstructive Pulmonary Disease

KEYWORDS: hypoxia, COPD, emphysema

PRINCIPAL INVESTIGATOR: Dillard, Thomas MAJ MC  
ASSOCIATES: Berg, Benjamin CPT MC

DEPARTMENT: Department of Medicine  
SERVICE: Pulmonary Disease Service

STATUS: Ongoing  
APPROVAL DATE: Jan 1988

FUNDING: Current FY: \$ 170 Previous FYs: \$ 0 Total: \$ 170

STUDY OBJECTIVE

The objective is to describe the hypoxic response to altitude simulation in COPD patients, to identify determinants, and to compare treatment modalities.

TECHNICAL APPROACH

The methods use hypobaric hypoxia to produce hypoxemia. Determinant variables are measured using pulmonary function tests at ground level and hypobaric hypoxia. Treatment with oxygen by 2 modes of delivery are evaluated at altitude conditions.

PRIOR AND CURRENT PROGRESS

Eighteen patients have been evaluated to date. Additional data collection to a total of 30 is planned. Preliminary analysis has been performed based on data collected.

CONCLUSIONS

Nasal cannulae produce greater arterial oxygen tensions than masks at comparable flow rates.

REPORT DATE: 01/02/90

WORK UNIT # 1725

DETAIL SUMMARY SHEET

TITLE: Evaluation of Inspiratory Parameters in the Response to Inhaled Bronchodilators

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rajagopal, Krishnan LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Pulmonary Disease Service

STATUS: Ongoing  
APPROVAL DATE: Feb 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To examine the effects of improvement in inspiratory measures on the relief in symptoms following the use of bronchodilator medication in patients with airflow obstruction.

TECHNICAL APPROACH

Pulmonary function tests will be performed before and after the inhalation of bronchodilator medications in patients with air flow obstruction. Inspiratory parameters will be examined and changes in these parameters will be correlated with changes in subjective symptoms.

PRIOR AND CURRENT PROGRESS

A computer program is currently available for the processing of test data and therefore patients will be recruited into the study during this year.

CONCLUSIONS

Work on this project can begin in the near future and can be completed on time.

REPORT DATE: 01/02/90

WORK UNIT # 1726

DETAIL SUMMARY SHEET

TITLE: Physiologic Assessment of Exercise Limitation in Upper Airway Obstruction

KEYWORDS: exercise, upper airways, lung mechanics

PRINCIPAL INVESTIGATOR: Rajagopal, Krishnan LTC MC

ASSOCIATES: Becker, Gregory CPT MC

DEPARTMENT: Department of Medicine

STATUS: Ongoing

SERVICE: Pulmonary Disease Service

APPROVAL DATE: Feb 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To examine the role of inspiratory muscle function in the limitation of exercise function.

TECHNICAL APPROACH

Patients with well defined upper airflow obstruction will have pulmonary function testing to determine resting inspiratory muscle function. Exercise testing will then be performed with monitoring of both inspiratory and expiratory airflow mechanics. the degree of inspiratory airflow reduction will be correlated with the degree of exercise limitation. Resting values will be used to derive predictors of exercise limitation.

PRIOR AND CURRENT PROGRESS

Three patients have completed the protocol. Additional patients with upper airway obstruction are being recruited into the study.

CONCLUSIONS

Satisfactory progress in the protocol to date. Should be able to complete the project on time.

REPORT DATE: 02/28/89

WORK UNIT # 1727

DETAIL SUMMARY SHEET

TITLE: The Effect of Caffeine on Bronchoconstriction Following Eucapnic Voluntary Hyperventilation of Dry Air

KEYWORDS: exercise-induced asthma, caffeine, airway hyper-reactivity

PRINCIPAL INVESTIGATOR: Phillips, Yancy LTC MC

ASSOCIATES: Duffy, Patrick CPT MC

DEPARTMENT: Department of Medicine  
SERVICE: Pulmonary Disease Service

STATUS: Ongoing

APPROVAL DATE: Mar 1988

FUNDING: Current FY: \$ 195 Previous FYs: \$ 0 Total: \$ 195

STUDY OBJECTIVE

The study is designed to determine whether or not ingestion of caffeine can interfere with the eliciting of a bronchospastic response in airway challenge testing.

TECHNICAL APPROACH

Subjects with demonstrated airway hyper-responsiveness to dry air hyper-ventilation are given either placebo or one of two doses of caffeine on three different test days. Patient and investigator are blind to the treatment condition. Pulmonary function testing is performed before and after challenge and the degree of bronchoconstriction is compared. Caffeine levels are drawn on all days.

PRIOR AND CURRENT PROGRESS

Twenty-two subjects have volunteered. Eleven did not have sufficient responsiveness to the challenge. Ten subjects have completed all three study days. One subject withdrew because of sympathomimetic side effects of caffeine after only one test day.

CONCLUSIONS

A preliminary analysis of the first seven subjects showed that in all instances the degree of bronchoconstriction to an identical challenge was reduced after ingestion of caffeine. The data are now being analyzed for all patients studied to date.

REPORT DATE: 04/05/89

WORK UNIT # 1728

DETAIL SUMMARY SHEET

TITLE: The Role of Respiratory Water Loss Without Heat Flux in Exercise-Induced Asthma

KEYWORDS: exercise induced asthma, respiratory heat loss, airway hyper-reactivity

PRINCIPAL INVESTIGATOR: Phillips, Yancy LTC MC

DEPARTMENT: Department of Medicine  
SERVICE: Pulmonary Disease Service

STATUS: Ongoing  
APPROVAL DATE: May 1988

FUNDING: Current FY: \$ 388 Previous FYs: \$ 0 Total: \$ 388

STUDY OBJECTIVE

The study aims to evaluate the effect of airway water loss in the absence of respiratory heat loss-on bronchoconstriction in subjects with exercise-induced asthma. This indirectly implicates the mechanism of airway hyper-reactivity in this population.

TECHNICAL APPROACH

Dry gas containing 5% CO<sub>2</sub> saturated with water at temperatures below 37 degrees C is then heated above body temperature. Specific combinations of water vapor and inspired temperature give conditions that are isenthalpic with alveolar gas (saturated at 37 degrees). The subject breathes this conditioned gas at 25 times FEV 1 for six minutes. PFTs are performed before and after and decreases in airflow are measured. Each subject will undergo testing with different gas conditions on 3 days in random order.

PRIOR AND CURRENT PROGRESS

The experimental apparatus (flow measures, thermocouples, and heat exchanger) have been assembled and calibrated. Normal subjects and subjects with exercise-induced asthma are now being recruited. No subjects have been studied to date.

CONCLUSIONS

The assembled apparatus can deliver conditioned gases at the required flow rates.

REPORT DATE: 05/08/89

WORK UNIT # 1729

DETAIL SUMMARY SHEET

TITLE: The Effect of Pre-Procedure Ipratropium or Metaproterenol by Metered Dose Inhaler on Pulmonary Function Following Fiberoptic Bronchoscopy

KEYWORDS: metaproterenol, ipratropium, bronchoscopy

PRINCIPAL INVESTIGATOR: Phillips, Yancy LTC MC

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DEPARTMENT: Department of Medicine  
SERVICE: Pulmonary Disease Service

STATUS: Ongoing  
APPROVAL DATE: Jun 1988

FUNDING: Current FY: \$ 0 Previous FYs: \$ 0 Total: \$ 0

STUDY OBJECTIVE

To compare to placebo the use of either inhaled ipratropium bromide or inhaled metaproterenol as single agents prior to fiberoptic bronchoscopy. The treatments will be evaluated by their effect on the requirement for supplemental oxygen during the procedure and for their efficacy in preventing the expected decrement in pulmonary function following bronchoscopy.

TECHNICAL APPROACH

Patients undergoing elective fiberoptic bronchoscopy (FOB) are solicited for participation. Prior to FOB pre and post screening spirometries using metaproterenol and ipratropium are completed. On the day for FOB, pre and post screening spirometries are completed using one of three inhalers. FOB is then done monitoring heart rate and oxygen saturation. A repeat screening spirometry is then completed following FOB. No modifications have been made to date.

PRIOR AND CURRENT PROGRESS

Eight subjects have been enrolled and this is the total to date as well. There have been no serious adverse reaction. One patient was withdrawn from the study following a transfusion reaction which resulted in an aborted FOB attempt. Benefit to patients has not been documented to date.

CONCLUSIONS

This protocol is ongoing presently. No conclusion has been made.